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Volume 6 — Number 3

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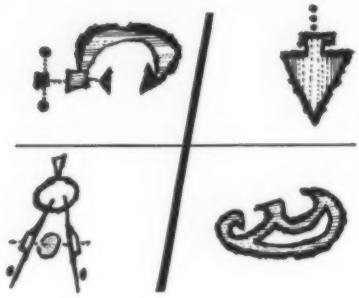

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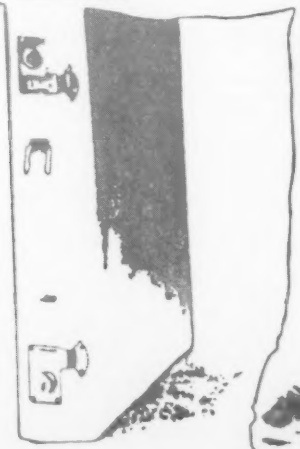

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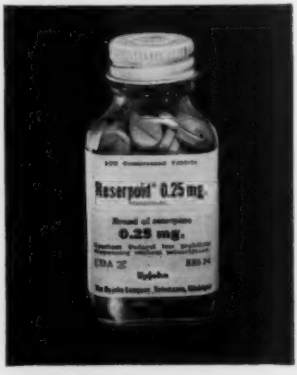

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1. Hollister, L. E., Krieger, G. E., Kringel, A., and Roberts, R. H.: Ann. New York Acad. Sc. *61*:92 (April 15) 1955. 2. Hoffman, J. L., and Konchegul, L.: Ann. New York Acad. Sc. *61*:144 (April 15) 1955. 3. Kline, N. S., and Stanley, A. M.: Ann. New York Acad. Sc. *61*:85 (April 15) 1955.

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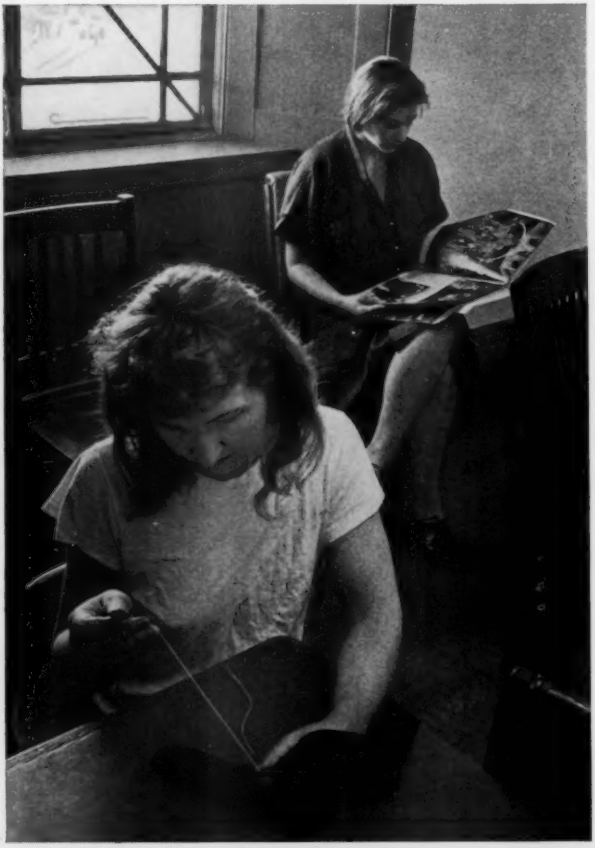

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1. Hoffman, J.L.: in Chlorpromazine and Mental Health, Philadelphia, Lea & Febiger, 1955.

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Volume 6 Neurology Number 3

Intracranial Tuberculomas

A Review of Clinical Features and Treatment

William A. Sibley, M.D. and Joseph L. O'Brien, M.D.

TUBERCLES and small tuberculomas within the substance of the brain are relatively common; indeed, the observations of Rich and McCordock[1] would indicate that they are the source from which the infection is disseminated in the vast majority of cases of tuberculous meningitis. On the other hand, tuberculomas of sufficient size to produce the symptoms and signs of an intracranial tumor are rare in the United States. In Cushing's series the incidence of tuberculomas among intracranial tumors was 1.6 per cent.[2] However, reports from Chile and India indicate that tuberculomas still represent 15.9 per cent and 20 per cent, respectively, of intracranial tumors in those countries.[3,4]

Regarded pessimistically by most neurosurgeons prior to the antibiotic era because of the high incidence of tuberculous meningitis following resection, tuberculomas can now be treated with greater success. Postoperative survivals of considerable duration have been reported with increasing frequency in recent years. Postoperative drug therapy has varied widely in recorded cases, especially with regard to dosage, method of administration, and duration of therapy. Decision as to duration of therapy is especially difficult, because autopsy statistics indicate that about 75 per cent of the untreated cases not succumbing to increased intracranial pressure eventually die of tuberculous meningitis.[5,6]

A review of the clinical and pathologic records at the Columbia-Presbyterian Medical Center from 1933 to 1955 reveals that 18 patients have had histologically verified tuberculomas of the brain with symptoms and signs of intracranial tumor during life. Small asymptomatic lesions discovered incidentally

From the Neurological Institute of Presbyterian Hospital, New York City.

at autopsy or in association with tuberculous meningitis were excluded from this study. These 18 cases comprise approximately 0.7 per cent of the brain tumors studied at the Neurological Institute during this period. An analysis of the clinical features in the 18 cases showed certain similarities and some interesting differences from previously reported series. Fifteen of these patients had a partial or gross total resection of the tuberculoma and eight received antituberculous drug therapy in the postoperative period. In an effort to determine the best method of management of these lesions, we have reviewed the postoperative treatment and results in 94 resected tuberculomas reported in the literature since 1947, making a total of 102 cases treated with antibiotics.

PATHOLOGIC FEATURES

The tumor is solitary in about 66 per cent of cases;[3,8] in 20 per cent of cases there are more than two tuberculomas present.[8] The pons is the site of a tuberculoma in 10 per cent of autopsied cases;[5] the remainder occur with about equal frequency in the cerebellum and in the cerebral hemispheres in both children and adults.[5,8] Tuberculomas behaving as intracranial tumors are usually several centimeters in diameter. Gonzalez-Revilla[7] reported the weights of the ten tumors which he removed surgically to vary from ten to 112 gm.

In the cerebellum almost all tumors are in contact with the pia due to the depth of the interfolial sulci and fissures, and infection is usually present beyond the gross confines of the tumor;[9] these two facts account for the virtual impossibility of total removal of cerebellar tuberculomas and explain why almost all of the successful removals without ensuing meningitis in the pre-antibiotic era were in cases of tuberculoma of the cerebral hemispheres.

In the cerebral hemispheres the tumors are usually deep and are said to be in contact with the surface of the brain in only about 20 per cent of cases.[9] Garland and Armitage[5] found the tuberculoma to be adherent to the dura in only 13 of 89 autopsied cases, but they seldom, if ever, arise from the dura.[9] Localized tuberculomas of the arachnoid, secondarily attached to the dura, occur uncommonly and may bear a gross resemblance to meningiomas.[5]

In the present series of 18 cases there were three instances of cerebellar tuberculoma, the remainder lying within the substance of the cerebral hemispheres; there was no site predilection in the latter location, anterior and posterior portions of the hemisphere being involved with about equal frequency (table 1). In the six autopsied cases of this group, all lesions were solitary with the exception of those occurring in cases 8 and 10 (table 1).

Histologically, the typical tuberculous granulation tissue is usually accompanied by varying degrees of caseation necrosis, especially near the center of the tumor. Calcification, when it occurs, is usually present in a concentric ring at the margins of the caseous central portion of the tumor.[12] Buchstein and Adson[9] found tubercle bacilli in appropriately stained sections of the lesion in all of 12 cases, but apparently only three of these were surgical specimens. Most authors do not record the frequency with which they are able to find tubercle bacilli in their surgical material, the only way of making an absolute differentiation from other granulomas, and we have been unable to find data on this point in

TABLE 1
CLINICAL DATA IN 18 CASES OF INTRACRANIAL TUBERCULOMA

Case	Year	Age	Duration of Symptoms	Major Symptoms	Location of Lesion	Proved by
1	1933	21	2 mo.	Headache, vomiting, right-sided seizures	Left temporo-occipital	Autopsy
2	1936	12	9 mo.	Headache, vomiting	Left cerebellum	Surgery
3	1937	31	1 yr.	Right hemiparesis, Right-sided seizures	Left frontoparietal	Surgery
4	1937	65	2 yr.	Headache, vertigo	Left cerebellum	Surgery
5	1940	16	10 yr.	Headache, left-sided seizures	Right parieto-occipital	Surgery and autopsy
6	1941	30	29 mo.	Headache, generalized seizures	Right occipital	Surgery
7	1942	40	1 yr.	Left hemiparesis	Right frontoparietal	Surgery
8	1943	21	11 mo.	Headache, generalized seizures	Left frontal and left cerebellum	Surgery and autopsy
9	1945	48	3 mo.	Headache, vomiting	Right temporal and right cerebellum	Autopsy
10	1945	65	4 mo.	Headache, vomiting, ataxia	Right frontal, pons, right temporal, left cerebellum	Autopsy
11	1947	55	1 yr.	Right-sided seizures	Left frontotemporal	Surgery and autopsy
12	1948	46	1 mo.	Headache, right-sided seizures	Left parietal	Surgery
13	1951	47	3 wk.	Right hemiparesis	Left frontoparietal	Surgery
14	1953	23	9 mo.	Headache, generalized seizures	Right temporoparietal	Surgery
15	1954	35	10 yr.	Right hemiparesis, right-sided seizures	Left frontoparietal	Surgery
16	1954	39	7 mo.	Left-sided seizures, ataxia	Right parietal	Surgery
17	1955	21	4 mo.	Headache, generalized seizures	Left parietal	Surgery
18	1955	49	8 mo.	Left-sided seizures	Left parieto-occipital	Surgery

the literature. It is evident, however, that specific identification of acid-fast bacilli may be quite difficult or impossible at times; for example, in two of our cases the organism could not be found in the surgical slides, but the tuberculous nature of the lesion was later proved at autopsy. In four cases acid-fast bacilli were found in the surgical specimens. Proof of the tuberculous nature of the granulomas was available in all of the autopsied nonoperated cases. Of the remaining cases, lymph node biopsy in two showed tuberculosis by guinea pig inoculation, one patient was later treated at another hospital for tuberculosis and died, and one patient had pulmonary tuberculosis; thus in these four cases the tuberculous etiology seemed virtually certain. In the other five cases in this series the diagnosis, although less certain, remains highly probable, supported by a typical histologic appearance with caseous necrosis, by failure to find other possible etiologic agents such as fungi, by negative spinal fluid serologic tests for syphilis in all cases, and by a strongly positive family history of tuberculosis in one patient.

While autopsy data indicate that about 75 per cent of patients with intracranial tuberculomas die of tuberculous meningitis and most of the remainder die of pulmonary or generalized tuberculosis,[5,6] the true frequency of spontaneous healing, with or without calcification, remains unknown. Gowers[11] estimated that this was not an uncommon occurrence, but more recent authors, on the basis of statistics indicat-

ing the rarity of calcification in confirmed tuberculomas and on the basis of reported cases in the literature, have suggested that spontaneous healing is distinctly exceptional.[5,10] The actual incidence of healed tuberculoma of the brain is not likely to be forthcoming, since such lesions tend to be asymptomatic during life, except possibly for seizures; at autopsy they may resist both bacteriologic and histologic proof of their former identity.[10] The following case, almost certainly representing a spontaneously healed tuberculoma, was not included in the present series of 18 cases:

A 48 year old white male was admitted to the Presbyterian Hospital in 1925 because of two months of severe headaches, with severe drowsiness for three days prior to admission. Investigation at that time disclosed only pulmonary tuberculosis, and he was discharged to a sanitarium. He was readmitted in 1932 because of generalized seizures for five hours prior to admission. Examination in the postictal state revealed only confusion and jargon aphasia which cleared slowly over a period of hours. He was then fairly well for four years, when he again began to have generalized seizures with a focal onset in the right arm; these occurred frequently for one month prior to his final admission. Examination now showed slight weakness of the right upper extremity and a right Babinski sign. He died following multiple seizures.

Autopsy disclosed bilateral pulmonary tuberculosis with cavitation. Section of the cerebrum showed a small fibrous nodule containing calcium in the left inferior temporal gyrus; there was no histologic hint of its former nature, and the rest of the brain showed no unusual features.

CLINICAL MANIFESTATIONS

Age incidence. The age distribution in the present series (table 1) was strikingly different from that usually reported in intracranial tuberculomas. The youngest patient was 12 years of age and the oldest 65 years. In the autopsied cases of Garland and Armitage,[5] over 50 per cent of the patients were under 10 years of age; 56 of 97 patients with intracranial tuberculoma presenting as tumors in Chile were under 20 years of age according to Asenjo and co-workers,[3] and half of Gonzalez' patients were children under 14 years.

The fact that only two of our cases were under the age of 20 is probably simply a reflection of the strikingly decreased frequency of tuberculosis in children in the United States in recent years.

Race. Ten of the 18 cases occurred in Negroes, reflecting the well known susceptibility of this race to tuberculosis. In South America it is apparently the aborigines, many recently urbanized, who show the same increased frequency of tuberculosis.[3]

Duration of symptoms. In 14 cases the first symptom attributable to the tumor was of less than one year's duration, but in only three cases was duration of symptomatology less than three months. Two cases had had difficulty for two to four years, and in two cases focal seizures had their onset ten years prior to admission.

Symptoms and signs. Fever was present preoperatively in only one case in the present series. Seizures and evidence of increased intracranial pressure were the usual clinical manifestations in the majority of cases.

Thirteen of our 16 patients with supratentorial tuberculomas had convulsions (81 per cent), and in eight of these the seizures were focal motor in onset (table 1). Ten of the 18 cases had papilledema. Asenjo and co-workers emphasized the fact that most of these patients present a syndrome of intracranial hypertension.[3] Papilledema was present in 82 of their

97 cases; these authors did not comment on the incidence of seizures in their patients, however.

Focal neurologic signs, of course, depend upon the location of the lesion and are not different from those produced by other intracranial mass lesions.

Extracranial tuberculosis. Nine (50 per cent) of the patients had negative chest roentgenograms, and five had roentgen evidence of pulmonary parenchymal tuberculosis, felt to be inactive in three. In another three patients, chest films showed only pleural thickening, and in one there was only widening of the mediastinal shadow.

Only 12 of the 70 patients (17 per cent) with tuberculomas in South America had normal chest roentgenograms.[3]

Laboratory findings. General blood and urine studies usually showed no significant abnormalities. Lumbar puncture was performed preoperatively in eight cases. Cell counts were normal in six of these, the other two showing a mild lymphocytic pleocytosis, with absence of meningitis. The spinal fluid sugar content was determined in only three instances and was normal in all three. Spinal fluid protein levels were elevated in seven cases, and were more than 100 mg. per 100 cc. in three. Thus cerebrospinal fluid findings were not dissimilar to those in other types of intracranial tumor.

Roentgenographic examination of the skull showed no specific diagnostic features. In 11 of the 18 patients skull films were normal; in five there was roentgen evidence of increased intracranial pressure; in one instance there was a shift of a calcified pineal gland. One case showed an enlarged sella turcica, earlier proved due to a coincident chromophobe adenoma of the pituitary. None of the tuberculomas showed roentgen evidence of calcification. Calcification in an intracranial tuberculoma is rare, occurring in from 1.3 per cent[8] to 2.5 per cent[5] of reported cases. When it occurs it is evidence of partial or complete healing.[12] The roentgen features of calcified intracranial tuberculomas have been reviewed in some detail by Weinberger and Grant.[13]

Diagnosis. It is evident from the foregoing that intracranial tuberculomas cannot be distinguished from other tumors prior to surgery or autopsy. The true nature of the tumor was diagnosed before operation in only one of the cases in the present series.

TREATMENT

Before Streptomycin

A survey of the literature by Van Wagenen[14] in 1927 revealed that, prior to that time, not more than 50 attempts at surgical removal of intracranial tuberculomas had been made. Permanent recoveries were rare and, with few exceptions, these occurred after the removal of a lesion from the cerebral hemisphere of an adult patient. Van Wagenen reported six more tuberculoma excisions; of these five were in cases of cerebellar tuberculoma and all died, usually within a three-month period, with a recurrence of symptoms accompanied by tuberculous meningitis. In 1937 Buchstein and Adson[9] were able to find only one case of survival after removal of a cerebellar tuberculoma. However, they collected 21 cases of complete surgical extirpation of cerebral tuberculomas, 15 surviving, with periods of observation up to nine years. Of the seven cases in our series subjected to excision prior to the use of streptomycin, there were three postoperative deaths from meningitis (cases 4,

5, 8, table 1) and one operative death (case 7); one died a year later of unknown cause (case 2); and two are still alive 18 years and 14 years after operation (cases 3 and 6, table 1).

It would appear, therefore, that the outlook following removal of cerebellar tuberculomas was virtually hopeless prior to antibiotics, while that following extirpation of a cerebral lesion was only slightly better. Because of the almost uniformly poor results of excision prior to the availability of specific drug therapy, many authors questioned the propriety of extirpation. For example, Cushing,[2] Van Wagenen,[14] and Horrax[16] recommended that only decompressive procedures be done when the nature of the lesion was discovered. Dandy[15] and Dott and Levin,[17] on the other hand, still favored total extirpation of tuberculomas. It would seem, however, that most surgeons followed the more conservative approach as demonstrated by Asenjo,[18] who did decompressions in 77 of 88 cases operated prior to streptomycin.

Surgery Combined with Antibiotic Therapy

With the appearance of streptomycin the results of attempts at extirpation of tuberculomas have greatly improved. We have made a survey of 102 cases, including eight of our own series, in which resection was combined with the use of antituberculous drugs. In the 102 cases there were 23 deaths, but only five of these fatalities were attributed to meningitis, although seven patients developed this complication in the postoperative period. The majority of deaths occurred as a result of the operation itself (table 2). Even with the short follow-up periods in some of these cases, it would seem that there has been a marked drop in the mortality rate from a figure which hovered close to 100 per cent, especially in cerebellar lesions, to a point where excision combined with the use of proper antibiotics is the treatment of choice.

TABLE 2
END RESULTS IN 102 INTRACRANIAL TUBERCULOMAS TREATED BY SURGICAL EXCISION AND ANTIBIOTIC THERAPY

Author	*Streptomycin Treatment*	*Follow-up*	*Cases*	*Survivors*	*Deaths*	*Cause of Death*	*Location of Tumors*
Herman and Garvey, 1947[19]	I.M. and I.T.	5-7 mo.	3	3	—	—	2 supratentorial, 1 infratentorial
Bernstein et al., 1950[22]	I.M. and I.T.	12 mo.	2	2	—	—	1 supratentorial, 1 infratentorial
Ivey et al., 1950[23]	I.M. and I.T.	17 mo.	1	1	—	—	1 infratentorial
Popov, 1951[21]	I.M. and I.T.	—	4	4	—	—	4 infratentorial
Tinsley and McCoy, 1952[20]	I.M.	—	4	2	2	1 meningitis, 1 operative	1 infratentorial, 3 supratentorial
Obrador et al., 1950[30]	I.M. and I.T.	To 18 mo.	15	12	3	1 general TB., 2 operative	10 infratentorial 5 supratentorial
Chandy and Isaiah, 1952[4]	I.M.	1-18 mo.	5	4	1	meningitis (cerebellar)	2 supratentorial, 3 infratentorial
Gonzalez-Revilla, 1952[7]	I.M.	12-36 mo.	10	7	3	2 meningitis, 1 another tuberculoma	6 supratentorial, 4 infratentorial
Descuns et al., 1954[24]	I.M. and I.T.	—	28	15	13	1 meningitis 12 operative	—
Asenjo et al., 1955[18]	I.M. (Isoniazid in 4)	3 yr.	22	21	1	—	—
Present series 1955	I.M. (Isoniazid and PAS in 6)	3-48 mo.	8	8	—	—	8 supratentorial

TABLE 3
POSTOPERATIVE TREATMENT REGIMENS IN 22 ADEQUATELY DOCUMENTED INTRACRANIAL TUBERCULOMAS NOT DEVELOPING MENINGITIS

Author	*Postoperative Antibiotic Therapy*	*Cases*	*Follow-up Time*	*Location*
Obrador et al., 1950[28]	Streptomycin: 1.0 gm. I.M. q.d. for 43-78 days; 0.05-.1 gm. I.T. for 28 days q.d.; then q.o.d. from 28th to 72nd day.	5	12-18 mo.	4 infratentorial; 1 supratentorial
Asenjo et al., 1951[3]	Streptomycin: 1.0 gm. I.M. q.d. for 80-100 days.	4	36 mo.	2 infratentorial; 2 supratentorial
Gonzalez-Revilla, 1952[7]	Dihydrostreptomycin: 1.0 gm. I.M. q.d. for 30 days, then 0.5 gm. I.M. q.d. for 42 days.	7	12-36 mo.	4 supratentorial; 3 infratentorial
Bernstein et al., 1950[23]	Streptomycin: 1.0 gm. I.M. q.d. for 90 days; 0.05 gm. I.T. q.d. for 14 days.	1	12 mo.	1 infratentorial
Present series	Streptomycin: 2.0 gm. I.M. q.d. for 12 and 28 days. PAS: 12.0 gm. q.d. for 30 days.	2	8 mo. 48 mo.	2 supratentorial
Present series	Streptomycin: 2.0 gm. I.M. q.d. for 30 days, then 1.0 gm. I.M. q.d. for 20 days.	1	24 mo.	1 supratentorial
Present series	Streptomycin: 2.0 gm. I.M. q.d. for 75 days. Isoniazid: 1.0 gm. q.d. for 75 days.	1	12 mo.	1 supratentorial
Present series	Streptomycin: 2.0 gm. I.M. q.d. for 15 days, then 1.0 gm. I.M. 3X weekly for 9 mo. Isoniazid: 0.3 gm. q.d. for 9 mo. PAS: 12.0 gm. q.d. for 9 mo.	1	18 mo.	1 supratentorial
	Total: 22 cases			10 infratentorial 12 supratentorial

The antibiotic regimens employed have varied considerably, but they all include streptomycin. A few of the cases have been treated in addition with p-aminosalicylic acid and isoniazid. While it would probably be desirable to institute antibiotic therapy preoperatively, this can only be done reasonably in those countries where tuberculomas comprise a high percentage of brain tumors,[18] since the diagnosis is rarely suspected before operation in other localities.

In 22 of the successfully treated cases which we have reviewed, sufficient information concerning details of postoperative antibiotic treatment was given and sufficiently adequate follow-up periods were recorded to allow reasonable evaluation. These cases not developing meningitis are summarized in table 3. The treatment regimens employed in the seven cases developing postoperative meningitis are shown in table 4.

Analysis of the 22 successfully treated cases shows that streptomycin in a dosage of 1.0 gm. intramuscularly daily for 60 to 90 days has been efficacious in the majority of instances in preventing postoperative meningitis. Three of the patients in our series, however, treated with 2.0 gm. of streptomycin for a lesser period of time also avoided meningitis. It is likewise evident that successful results have occurred with and without intrathecal streptomycin (tables 2 and 3).

Among the seven patients developing meningitis, the meningitis had its onset during the treatment with 1.0 gm. of streptomycin daily in one patient in our series and in one of Gonzalez' patients receiving dihydrostreptomycin.[7] The other five cases developing meningitis were treated either with less than 1.0 gm. daily or for less than 60 days.

Thus it would seem unnecessary to treat these patients postoperatively for longer than 60 to 90 days with daily streptomycin, especially now that isoniazid is available for concurrent use. The optimum duration of therapy with isoniazid and p-aminosalicylic acid cannot

TABLE 4
REPORTED CASES DEVELOPING POSTOPERATIVE MENINGITIS

Author	*Treatment and Duration*	*Number of Cases*	*Location of Lesion*	*Onset of Meningitis*
Popov, 1951[23]	Streptomycin: 0.9 gm. q.d. for 30-90 days; 0.1 gm. I.T. q.d. for 30-90 days.	1	infratentorial	—
Tinsley and McCoy, 1952[29]	Streptomycin: 0.5 gm. q.d. I.M. for 42-56 days.	1	infratentorial	—
Gonzalez-Revilla, 1952[7]	Dihydrostreptomycin: 1.0 gm. I.M. q.d. for 30 days; then, 0.5 gm. I.M. q.d. for 42 days.	1 1	supratentorial supratentorial	29th day 48th day
Chandy and Isaiah, 1952[4]	Streptomycin: 1.0 gm. I.M. for 40 days.	1	infratentorial	60th day
Descuns et al., 1954[25]	Streptomycin: 1.0 gm. in surgical cavity; then intrathecal therapy for 30 days.	1	infratentorial	—
Present series, 1955	Streptomycin: 1.0 gm. I.M. q.d. Isoniazid: 0.6 gm. q.d.	1	supratentorial	7th day
		Total: 7 cases	4 infratentorial 3 supratentorial	

be stated from the cases which have been reviewed. Lumbar puncture should be done at weekly intervals, at least for the first two to three months after operation, even in the absence of overt symptoms of meningitis. If clinical symptoms or spinal fluid evidence of tuberculous meningitis supervene, then, of course, treatment is continued for much longer periods, in accordance with the present concepts of the therapy of tuberculous meningitis.[27,28] Although postoperative therapy with daily streptomycin may be continued for longer periods than three months in the absence of meningitis, this course appears to have no definite advantage on the basis of available data, and would enhance chances of drug toxicity and development of bacteriologic resistance.

SUMMARY

1. Intracranial tuberculomas behaving as brain tumors occur rarely in the United States at present, but still represent a large proportion of intracranial mass lesions in many parts of the world.

2. The clinical features of 18 cases of intracranial tuberculoma studied at the Columbia-Presbyterian Medical Center since 1933 were not dissimilar from those of other brain tumors, and diagnosis is therefore difficult before operation. Seizures and increased intracranial pressure were present in the majority of cases.

3. The over-all mortality rate in 102 collected cases treated with a combination of surgical excision and postoperative streptomycin therapy was about 22 per cent, representing a striking improvement in results since the introduction of specific drug therapy.

4. The development of tuberculous meningitis in the postoperative period has been prevented in almost all cases by daily streptomycin therapy continued for 60 to 90 days after operation. Treatment for longer periods of time, in the absence of meningitis or extracranial tuberculosis, probably has no definite advantages and certain definite disadvantages. Isoniazid and para-aminosalicylic acid should be used in addition to streptomycin, although few cases so treated have been reported as yet and the optimum duration of therapy with these drugs cannot be stated.

5. Frequent spinal fluid analyses should be performed for several months

postoperatively. Evidence of meningitis dictates more prolonged therapy in accordance with modern concepts of the treatment of that disease.

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Sensory Loss With Poliomyelitis

Fred Plum, M.D.

PAIN AND CUTANEOUS HYPERALGESIA are common in acute poliomyelitis, while loss of sensation is rare. Levaditi, Pignot, and Leoneano,[1] however, reported the autopsy findings on a 34 year old man whom they diagnosed as having poliomyelitis. He had died on the fourth day of a febrile illness with ascending paralysis and loss of sensation in the legs. The anterior and posterior horns of the spinal cord were infiltrated with hemorrhagic and inflammatory foci, and nerve cells were equally degenerated in both anterior and posterior horns. There were hemorrhagic foci in the cord white matter and neuronolysis in the dorsal root ganglia. Inoculation of a filtrate of spinal cord into the abdomen of a Macacus sinicus monkey was not followed by disease in the monkey, although the animal was later proved susceptible to poliomyelitis virus. Sachs[2] and Lloyd[3] reported individual patients with acute motor and sensory transverse myelitides attributed to poliomyelitis virus. Evidence for poliomyelitis in Sachs' patient consisted of a single positive serum poliomyelitis neutralization test, while Lloyd's case was considered to be poliomyelitic principally on the grounds that it occurred during a poliomyelitis epidemic. Strümpell[4] observed a 19 year old male six months after an attack of acute poliomyelitis. In addition to residual atrophic paralysis of the right and left arms and left hip, the boy had reduced sensation to pain and temperature below segment T_3 on the left and from T_3 to T_6 on the right. Strümpell postulated that poliomyelitis had caused lesions in the posterior gray columns resulting in this syrinx-like clinical picture. Wickman[5] cited one case of poliomyelitis from his extensive series who had "distinct diminution" of pain and temperature sensation in the legs, the sensory changes persisting for over a year. He refers to patients with similar changes observed by Krause[6] and Müller.[7] Pathologic observations are lacking in all of these cases. Little clinical detail was given by Schaller[8] in describing a patient thought to have acute poliomyelitis who suffered "questionable" hypesthesia transiently in the thighs associated with paralysis of both legs. Hüuerman[9] described a 14 year old boy with a complete thoracic transverse myelitis. Because of fever and 26 cells in the spinal fluid the diagnosis of poliomyelitis was made. The child recovered, apparently without residua, in three months. Bell[10]

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described the pathologic changes in a 23 year old woman who died 21 months after the onset of acute poliomyelitis. She was reported to have "hypesthesia to light touch in the skin of her legs" during her acute illness, but subsequent sensory examinations were not noted. At autopsy the anterior horn cells of the spinal cord were "completely destroyed." In addition, there was "demyelination and gliosis of portions of the posterior columns at all levels . . . (and) . . . scattered demyelination in the lateral and anterior columns." The dorsal root ganglia were not described.

The older classification of a polyneuritic form of poliomyelitis was applied by most workers to illnesses in which severe pain and nerve tenderness were seen. Schäfer and Walther,[11] however, felt that this diagnosis applied to five children seen during a poliomyelitis epidemic who had fever, cerebrospinal fluid pleocytosis, and sensory loss in the legs, with largely symmetric motor weakness. All these children recovered completely in two months, which is unusual in poliomyelitis. Sandifer[12] presented to the Royal Society of Medicine a 30 year old man diagnosed as having poliomyelitis. He had fever, spinal fluid pleocytosis, and "lower motor neurone" paralysis of his arms. Five days after onset of illness, complete flaccid paralysis of the legs with a complete sensory loss to the "groins in front, buttocks behind" developed suddenly. Three months later partial asymmetric return of muscle function was observed in the arms, but the neurologic deficit in the lower extremities was unaltered. McAlpine, discussing Sandifer's paper, stated he had seen "about half-a-dozen cases of acute myelitis" in poliomyelitis but did not detail the findings.

Because of the rarity with which it is seen clinically and because of the tenuousness of the evidence upon which the diagnosis of poliomyelitis was made in some of the above reports, we had believed until recently that significant sensory loss militated against the diagnosis of poliomyelitis. Two patients have been observed within the past three years, however, who had acute illnesses similar to acute poliomyelitis except that in addition they suffered sensory loss in the lower extremities. Following her acute illness, one of these patients passed type I poliomyelitis virus in her stool and showed a rising neutralization titer to this virus in her serum.

CASE REPORTS

Case 1. A 27 year old male was admitted to the King County Hospital on August 19, 1951. He had been well until two days before, when he developed stiff neck, stiff back, anorexia, and fever. The day before admission he vomited, felt generally ill, and by evening noted "tingling" in the feet, plus leg weakness. At 5:00 a.m. on the day of admission, he awakened to find he was unable to move his legs. He had difficulty in getting a satisfyingly deep breath. He had last voided at 9:00 p.m. the previous day and thereafter he was unable to initiate micturition.

In the hospital he had a temperature of 101.8° F. His left pupil was 2 mm., his right 3 mm. Swallowing was slightly impaired. His neck was rigidly stiff, lateral motion of the neck was moderately reduced, and there was weakness in both triceps, the left deltoid, the left hand, both sets of intercostals, and the abdominals. There was complete flaccid paraplegia of the lower extremities. All modalities of sensation were reduced caudal to the L_2 dermatome bilaterally, the loss being greatest in the more caudal dermatomes, with position and vibration absent in the feet and other sensory modalities markedly reduced in the perianal area.

Laboratory work showed a white blood count of 9,100 per cu. mm. with an essentially normal differential. His spinal fluid was under an

initial pressure of 280 mm. There were 669 cells per cu. mm., of which 58 per cent were polymorphonuclear neutrophils, and the spinal fluid protein content was 125 mg. per cent. Spinal fluid cultures and other laboratory studies were negative.

A catheter was inserted to relieve the urinary retention. Over the course of a few hours following admission, swallowing difficulties increased, breathing became labored, and respirations declined in depth, with the rate increasing to 35 per minute. A tracheotomy was done and the patient was placed in a respirator the evening of admission. Over the next two days he had progression of paralysis; the swallowing function disappeared completely, and he was able only to flex the fingers of both hands and to pronate and supinate the right forearm. By August 25, six days after admission, he had developed a 6 by 5 cm. shallow decubitus over the sacral area. He was still severely ill and sensory examinations were performed only with difficulty, since the patient was in the respirator constantly. Nonetheless, sensory loss appeared to have increased over the feet but the sensory level had not risen above L_5. On August 30 he developed abdominal distention, and gastric intubation followed by aspiration yielded an estimated 400 to 500 cc. of coffee ground material. Guaiac positive stools were passed shortly afterward. Gastrointestinal bleeding continued for the next 48 hours. By September 2 he began to improve gradually and his body temperature returned to normal ranges. Swallowing function returned on September 14, and by mid-October transfer to a cuirass respirator was begun although he was able to breathe independently only a few minutes at a time. On October 23 he was transferred to a Veterans Hospital for further convalescent care; he was eventually discharged to his home in October 1952, still requiring artificial respiration for sleeping.

The patient was later admitted to the Northwest Respirator Center on October 18, 1953 because of recurrent urinary tract infections and acute hypopotassemia, the latter having so intensified his weakness that he again required artificial respiration constantly. Examination after correction of the electrolyte depletion and restoration of his strength showed normal cranial nerve function. He had asymmetric, atrophic, flaccid paralysis of the neck muscles, both shoulder girdles, both deltoids, the left biceps and triceps, the left supinator and pronator, the right biceps, both opponens muscles, the major part of the intrinsic thenar group of the right hand, and the right wrist extensors. Paralysis and wasting also involved all of the intercostals except the left third and right sixth, the right trunk flexors and extensors, and all muscle groups below the waist except for the external rotators of the left hip, the extensor of the left knee, and the flexors of the left foot, in which slight motion was detected. Fluoroscopic examination of the chest showed a paralyzed right diaphragm with paradoxical activity, as well as limitation of left diaphragmatic movement to two interspaces on deep inspiration. Examination of sensory functions was normal down to the L_5 dermatome. From L_5 to S_3 there was a progressive reduction in the sensations of pain, touch, temperature, and position with severe loss of these modalities in the segments caudal to S_3 (figure 1). Vibratory sensation (C 256) was lost below the femoral necks.

The tracheostoma was still open with a prosthetic plug in place. He had a large sacral decubitus and a right renal calculus was demonstrated by roentgenogram. Subsequently the hypopotassemia was demonstrated to have resulted from excessive washout of potassium by frequent large volume enemas. During hospitalization the renal calculus was removed, the

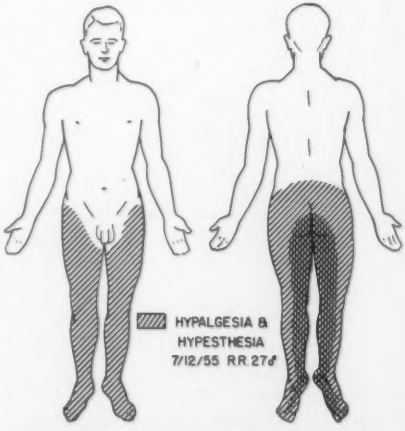

FIG. 1. *Case 1.* Areas of reduction and loss of sensation. The more darkly shaded areas represent more severe sensory loss.

decubitus was successfully repaired surgically, and bowel care training eliminated the excessive electrolyte wastage.

The patient has been out of the hospital and working as a civil engineer for the past year, although he still sleeps on a rapid rocking bed because of limited ventilatory ability. Neurologic findings in July 1955 were unchanged from those recorded in October 1953.

Case 2. A 36 year old woman was admitted to the King County Hospital on October 21, 1954. One week previously she had had low grade fever, sore throat, and diffuse muscle aching which lasted 36 hours. Two days before admission she developed pain in the back and legs, general feelings of ill health, diffuse headache, and a sense of feverishness. The day before admission she noticed weakness in her toes. This weakness later rose to involve the entire lower extremities. Twelve hours later pins and needles paresthesias appeared in her feet and gradually ascended to thigh level.

On examination she was flushed, apprehensive, and had a temperature of 100° F. She had a stiff neck, tremulousness of the tongue and upper extremities, and flaccid paralysis of both lower extremities, with acute urinary retention. Tendon reflexes were active and equal in the upper extremities, absent in the lower extremities. The superficial abdominal reflexes were intact. Cutaneous hyperalgesia was observed across the back and down the legs in the distribution of approximately the L_4 dermatome. All modalities of sensation were progressively reduced caudal to this level, with vibratory and position sense absent in the feet (figure 2). Spinal fluid was under a pressure of 210 mm. and contained 356 white cells per cu. mm. (49 per cent polymorphonuclear neutrophils) and 160 mg. per cent of protein. The white blood count was 18,000 per cu. mm., with 84 per cent neutrophils. Cultures of the spinal fluid as well as other special studies were negative.

She gradually developed intercostal muscle paralysis during the next two days, with weakness about the right shoulder and in the right diaphragm. Her vital capacity (predicted normal 3,250 cc.) fell from 2,100 on admission to 900 cc. on October 24, and on that date she became partially disoriented and complained of diplopia on either lateral gaze. She was observed to have bilateral medium grade nystagmus on lateral gaze, flaccid weakness in both deltoid muscle groups, diffuse flaccid paralysis in the right arm, asymmetric intercostal paralyses, and reduction of diaphragmatic function bilaterally. Her respiratory rate rose to 32 per minute by the evening of October 24. Irregularities of rate and depth of breathing then appeared and she was placed in the body respirator. Swallowing paralysis developed during the next 24 hours, and on the morning of October 26 a tracheotomy was performed in order to maintain the airway.

She began improving from this point and by November 1 was able to breathe without the respirator for brief periods, having a vital capacity of 220 cc. Two days later swallowing function began to return and respiratory function gradually improved. She required progressively less ventilatory aid until January 10, 1955 when artificial respiration was discontinued entirely. The tracheotomy was removed December 16, 1954. Repeated muscle evaluation during convalescence showed asymmetric weakness of the neck and upper extremities, poor function in the scapular groups, and complete symmetric paralysis of the lower trunk muscles and the lower extremities. Fluoroscopic examination of the chest early in convalescence showed little or no diaphragmatic function on the left and diaphragmatic excursion of one interspace on the right. Early convalescence was marked by considerable spontaneous pain in the lower extremities with burning and itching of the skin. She also experienced severe stretch pain and burning afterpains to pricking cutaneous stimuli in the dermatomes below L_4.

Spinal fluid examinations on November 10, 1954 showed an initial pressure of 260 mm., with 12 monocytes per cu. mm. and 84 mg. per cent of protein. Spinal fluid examination on December 8 showed an initial pressure of 78, with 3 monocytes per cu. mm. and 42 mg. per cent of protein. Cystometric examinations repeatedly showed an atonic bladder in which filling sensation was reduced and reflex activity was reduced to absent.

Early hospitalization was complicated by severe intestinal hypomotility and the patient's first stools were not obtained until November 21 and 24. Type I poliomyelitis virus was isolated by tissue culture from both these stools. Poliomyelitis antibody studies on sera drawn on October 21 and November 19, respectively, showed a rise in serum neutralization titer to type I poliomyelitis from 12 to 64, a rise in

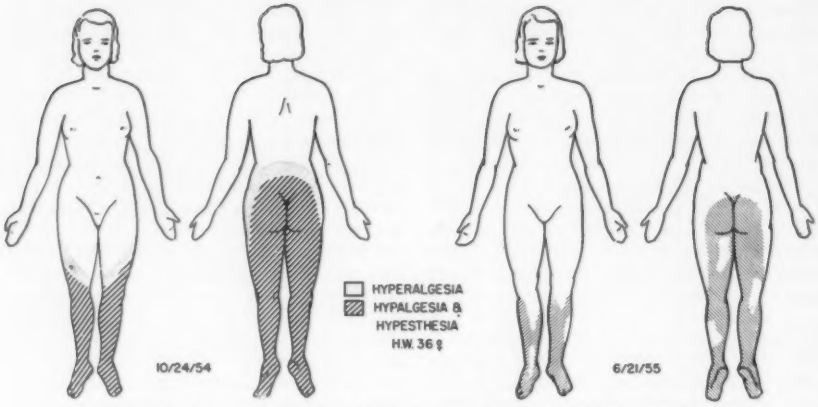

FIG. 2. *Case 2.* Areas of sensory loss during the acute illness (10/24/54) and eight months later. Note islands of normal sensation in later examination.

type II titer from less than 4 to 6, and a type III antibody titer which remained constant at 160.

Thresholds for sensation in the involved areas gradually improved so that by June 1955 hyperalgesia had disappeared and hypalgesia was only moderate in degree. The sensory level, as diagrammed in figure 2, was still approximately at the L_4 dermatome, but there were islands of normal sensation within the area of sensory loss. Vibratory and position sense were reduced below the knees and marked sweating was observed in the feet. Examination of motor function showed considerable but asymmetric return in muscle power in the trunk and upper extremities above the sensory level. There was flaccid atrophic weakness of the right paraspinal cervical groups, the left triceps, the right deltoid, the left rectus abdominus, and left abdominal oblique. Tendon reflexes in the upper extremities were moderately hyperactive; superficial abdominal reflexes were absent, as was all reflex activity in the lower extremities. No movement had returned in the severely atrophic lower extremities.

DISCUSSION

These two patients had similar illnesses. The problem is whether illnesses accompanied by such extensive sensory abnormalities could be attributed to acute poliomyelitis. Both patients were hospitalized during periods of peak poliomyelitis incidence and had febrile diseases with spinal fluid pleocytosis and rapidly progressing paralysis which reached a maximum three to four days after onset. Paralysis above the sensory level was asymmetric, flaccid, followed by muscle atrophy, and marked by variable recovery in different muscle groups. Except for their sensory abnormalities, their diseases were clinically typical of paralytic poliomyelitis. Isolation of virus from the stools combined with a rising antibody titer to the same virus strain in the serum was proof of recent poliomyelitic infection in case 2. It seems probable that her clinical disease was due to this infection and that case 1 similarly suffered this unusual effect of the virus.

Earlier clinical observations on sensory changes in poliomyelitis have already been reviewed. Damage to sensory neurons also has been demonstrated repeatedly in human and experimental studies of the pathology of the disease.

Thus, Forssner and Sjövall,[13] as well as Peabody and Draper,[14] called attention to scattered neuronolysis in posterior root ganglia. Sabin,[15] Staemmler,[16,17] Brass and Brückel,[18] and others confirmed and extended these observations. Staemmler, in particular, reported extensive neuronolysis and neuronophagia in occasional ganglia. Although demyelination of dorsal root fibers has not been reported in human cases, O'Leary and co-workers[19] observed degeneration and impairment of conduction of the majority of the fibers in a sacral sensory root of one of their monkeys (No. 57) with poliomyelitis. Other sensory roots in the animal were not removed for analysis. Within the central nervous system, damage to sensory neurons with poliomyelitis ranges from cellular loss in the posterior intercalated neurons and Clarke's column in the spinal cord to similar abnormalities of the sensory nuclei of the thalamus.[15,20,21]

The sensory defects in these two cases involved all modalities, although vibration and position sensations were affected most. Paresthesias, itching, and burning were felt in the damaged sensory areas during convalescence. Loss of motor power was nearly complete in these segments where sensation was impaired. Either a diffuse myelopathy of the lumbosacral cord or extensive neuronal necrosis in dorsal root ganglia and ventral horn cells could have caused these sensorimotor defects. The symmetric distribution of the sensory loss and the abrupt transition from normal sensation to involved dermatomes suggested a myelopathy. Neuronolysis of dorsal root ganglia is frequent in poliomyelitis, however, and this appears to be the more likely process. In experimental poliomyelitis, lesions of posterior horns and spinal ganglia are found especially in those neural segments in which severe involvement of anterior horns occurs.[22]

Prolonged intense pain is seldom experienced in poliomyelitis except in association with severe paralysis. The lower extremities are more often paralyzed completely and are more frequently the site of such pain than are other body regions. These manifestations may reflect lesser degrees of the same pathologic process which affected these two cases. Pathologic abnormalities in motor cells often exceed clinical paralysis in poliomyelitis. The same physiologic reserve in sensory neurons would explain why clinical sensory loss so seldom reflects the damage to sensory ganglia in this disease.

SUMMARY

Two patients are described who suffered severe sensory loss in lumbosacral dermatomes during clinical illnesses otherwise typical of acute poliomyelitis. Type I poliomyelitis virus was isolated from the stools of one of these patients, who also showed a rising antibody titer to the virus in her serum. The clinical changes observed could have been caused by either a diffuse myelopathy of the lumbosacral cord or extensive damage to dorsal root ganglion cells combined with necrosis of anterior horn cells in the same neural segments. Neuronolysis of the dorsal root ganglia is regarded as the more likely cause of the sensory loss because of the frequency with which pathologic abnormalities are found in these ganglia in human and experimental poliomyelitis.

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■ If we divide transversely, in the dorsal region, the two posterior columns of the spinal cord in a mammal, we find that its voluntary movements seem not to be at all disturbed or diminished. If in another mammal we divide transversely the whole of the spinal cord, except the posterior column, we do not find the least appearance of a voluntary movement in the muscles which receive their nerves from the parts of the spinal cord which are behind the section. So far, therefore, as the posterior columns alone are concerned, we arrive at a positive, and, I think, undeniable conclusion, which is, that the posterior columns of the spinal cord are not directly employed in the conveyance of the orders of the will to muscles.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System,* published in 1860.

Effect of Mesencephalic Lesions on Metrazol-Induced Cortical Activity

David A. Freedman, M.D. and Gregory S. Ferriss, M.D.

IT HAS BEEN reported previously[1] that restricted lesions in the rostral mesencephalic reticular formation result both in marked increase in the threshold for electrically-induced cortical seizures and in the loss of the ability of the cortex to respond with sustained hypersynchronous activity. The present study was undertaken to determine the effect of similarly placed lesions on the capacity of Metrazol to induce seizure activity.

EXPERIMENTAL PROCEDURE

Fifteen adult cats were used in these experiments. At the time of stimulation the animals were unanesthetized and under artificial respiration. Preliminary surgery, including tracheotomy, section of the spinal cord at C1, and removal of the calvarium, was carried out under ether anesthesia. Each animal was mounted in the frame of the Horsley-Clarke apparatus, and silver ball electrodes measuring 1 mm. in diameter were placed on the dura approximately over the coronal, lateral, and postsylvian sulci. Metrazol, in solutions containing 10 mg. per ml., was injected through a polyethylene catheter threaded into the femoral vein. Using the Jimenez-Castellanos atlas[2] as a guide, electrolytic lesions were placed in the rostral mesencephalon. All lesions were verified histologically.

OBSERVATIONS

Effect of Metrazol on the electroduragram in the presence of an intact brainstem.

1. Latency.

Under the experimental conditions already described, the latent period between the injection of Metrazol and the first "seizure type" cortical response varied between five and 20 seconds. In most cases some change was noted in the record in less than ten seconds.

2. Seizure patterns.

Within a group of animals of average weight (2.5 to 4.0 kg.), it was not possible to correlate the threshold dose for cortical seizure activity with body weight. Ten to 15 mg. of Metrazol consistently produced some high voltage seizure activity. This consisted of either random spikes or bursts of spikes

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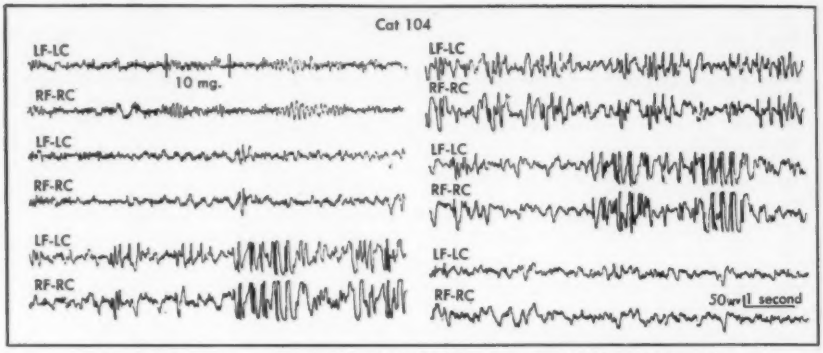

FIG. 1. The response of a cat with an intact brainstem to a threshold dose of Metrazol.

and/or slow waves (figure 1). Such a response usually persisted for ten to forty seconds and was followed by random seizure discharges for as many as 15 to 30 minutes after the injection (figure 2).

Twenty to 30 mg. of Metrazol injected in the same manner produced a characteristic pattern. There was an abrupt onset of high voltage activity which affected all cortical areas simultaneously (figure 3). This was followed by intermittent spikes, slow waves, and low voltage fast activity which stopped abruptly and was replaced by a prolonged isoelectric period (figure 4). The latter was finally interrupted by random spikes and slow activity which gradually increased in amount and merged into the pattern of the resting record. The picture was strikingly similar from all areas of the cortex. Jasper and Erickson,[3] who have noted this symmetry of response, very appropriately characterize it as "like the turning on and off of a switch."

A single injection of 50 to 100 mg. of Metrazol yielded repetitive alternations of high voltage seizure activity and isoelectric periods following the pattern described above (figure 5). Such persistent abnormalities have been observed for as long as two hours after a single such injection. The experiment was terminated at this time although the abnormality persisted. Jasper and Erickson have also observed this phenomenon.

3. Effect of subliminal doses of Metrazol.

Repeated injections of 5 mg. of Metrazol at five minute intervals over a 30-minute period (total of 35 mg.) yielded no change in the resting record.

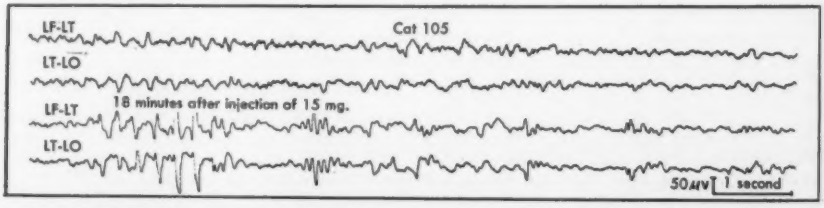

FIG. 2. Persistence of paroxysmal activity following a single threshold dose of Metrazol in the presence of an intact brainstem.

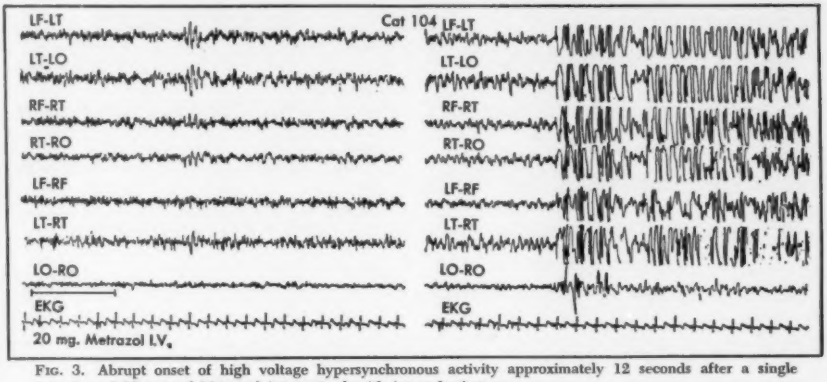

FIG. 3. Abrupt onset of high voltage hypersynchronous activity approximately 12 seconds after a single injection of 20 mg. of Metrazol into animal with intact brainstem.

Effect of Metrazol in the presence of mesencephalic lesions.

Figure 6 shows a typical mesencephalic lesion. Our objective was to sever the diencephalomesencephalic connection of the reticular formation. In the presence of such lesions the following observations were made.

1. Latency.

No change was noted in the latency of the cortical response to liminal doses.

2. Seizure patterns.

There seemed to be a moderate increase in the threshold of the cortex to Metrazol-induced seizure activity. Minimal electroencephalographic changes similar to those shown in figure 1 required injection of at least 30 mg. of Metrazol where they were previously obtained with 10 to 20 mg.

Single seizures with high voltage hypersynchronous activity like those shown in figures 2 and 3 could not be obtained. Increased doses of Metrazol yielded only increased amounts of random spike and slow activity (figure 7) until doses of the order of 100 mg. were utilized. At this level persistent seizure patterns were

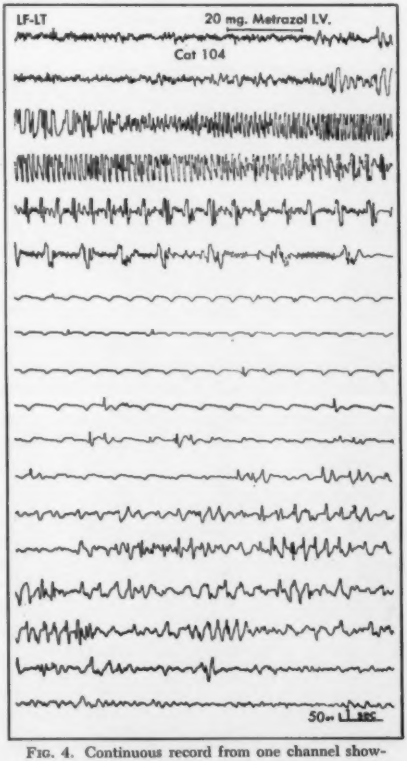

FIG. 4. Continuous record from one channel showing the course of a seizure induced in an animal with an intact brainstem by the injection of 20 mg. of Metrazol.

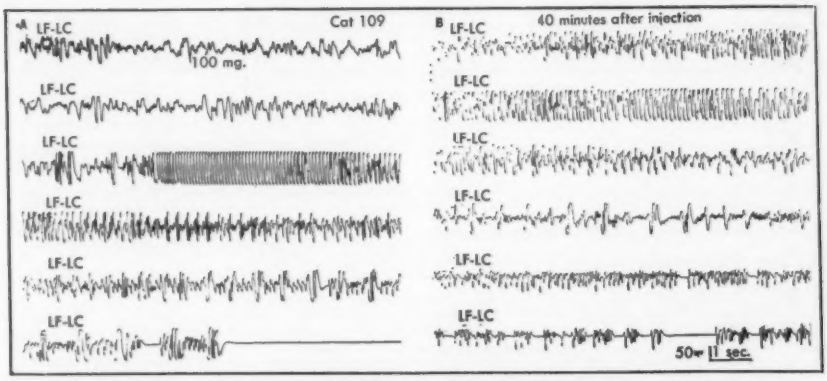

FIG. 5. Persistence of electrical abnormality following a single injection of 100 mg. of Metrazol into an animal with an intact brainstem.

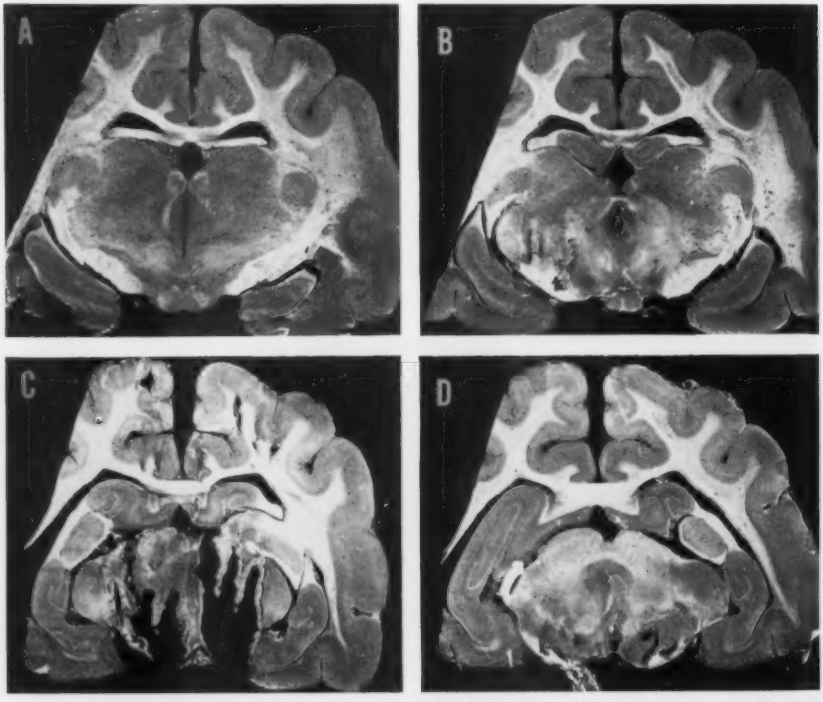

FIG. 6. Typical mesencephalic lesion: *A*. Intact posterior diencephalon. *B*. Most rostral extent of lesion. *C*. Maximal extent of lesion. *D*. Caudal extent of lesion.

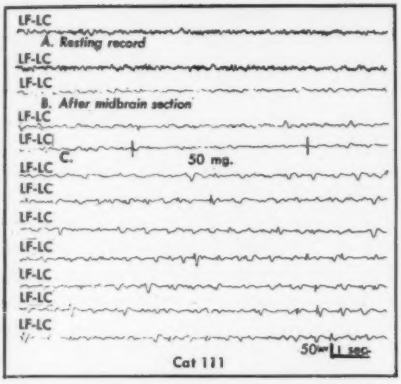

FIG. 7. Response of animal with mesencephalic section to 50 mg. of Metrazol (compare figures 1 and 2).

elicited. These, however, were strikingly different from the seizures elicited in the presence of an intact brainstem (figure 8). The abrupt onset of high voltage hypersynchronous activity noted following the injection of Metrazol into an animal with an intact brainstem did not occur here. Intermittent isolated spikes and slow waves of high amplitude were followed by isoelectric periods in the same manner as noted in animals without mesencephalic lesions. However, high voltage hypersynchronous activity occurred only after ten or more minutes and then only in brief bursts of one or two seconds' duration. The protracted persistence of the response to Metrazol noted in the intact animals was also observed in these preparations.

DISCUSSION

Several papers[3–8] published during the era of Metrazol treatment of major psychoses, as well as more recently,[9] report electroencephalographic changes similar to those seen in our animals with an intact encephalon. Phenomena such as the noted latency of response, repetitive character of the discharge, and striking isoelectric periods have all been described previously. Goodman and his co-workers[10] suggest that Metrazol exerts its long lasting effects by virtue of its persistence within the nervous system. Were this the case, repeated subliminal injections should have a cumulative effect. This proved not to be the case in our experiments. We suggest, therefore, that the persistent effect of a single liminal injection of Metrazol must be the result of changes within the nervous system produced by a substance which is itself only briefly available.

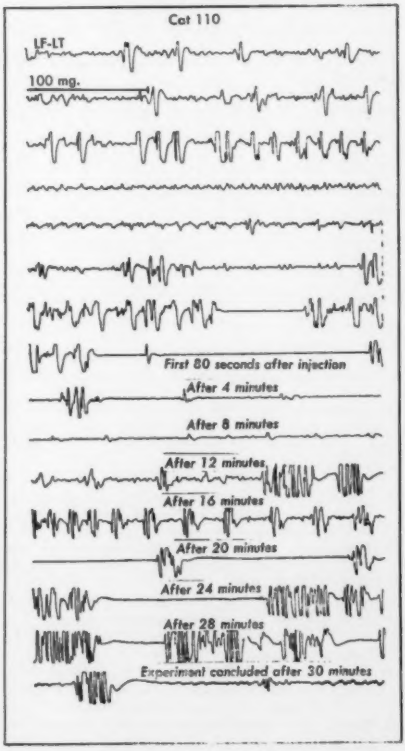

FIG. 8. Response of animal with mesencephalic lesion to 100 mg. of Metrazol (compare figure 5).

Freedman and Moossy[1] point out that acute lesions of the mesencephalic reticular formation act to reduce the capacity of the cortex to respond to electric shock with sustained hypersynchronous activity. The seizures they elicited were consistently brief in duration and lacking in the high voltage hypersynchrony noted when the midbrain was intact. By contrast the duration of abnormality following the injection of Metrazol is not reduced by section of the brainstem. The intensity and persistence of the hypersynchronous activity are markedly reduced, however. There are then both similar and dissimilar features in the response of the cortex to these forms of stimulation after midbrain section. Electric shock is evidently an evanescent agent which initiates a chain of events within the nervous system. Metrazol, on the other hand, by virtue of its capacity to lower threshold for a protracted period of time, yields persisting alterations in the cortical response. In both cases the pattern of the cortical response must necessarily be a function of the available neural connections. Our data suggest that, whatever the nature of the stimulating agent, the presence of an intact brainstem is required to elicit sustained high voltage high frequency discharges. Such an inference is consistent with the conception of the mesencephalic reticular formation as a facilitating area with respect to such more rostral structures as the cerebral cortex. It should be added, however, that this does not contradict the conclusion advanced by Starzl and co-workers[9] that the Metrazol-induced seizure has its origin in the cerebral cortex. We are dealing here with a factor which has to do with the pattern of a seizure rather than its initial phase. Wherever the initial discharge may occur, it would appear that the reticular formation is necessary for the maintenance of a sustained hypersynchronous pattern.

CONCLUSIONS

The data presented suggest that Metrazol is a rapidly acting toxic substance which produces long lasting depression of the threshold of the cells of the central nervous system. The precise pattern of cerebral activity which results from such a depression depends on the nature of the available cellular interconnections. Where the cortex is isolated from the mesencephalic reticular formation, there results a loss of capacity for it to respond with sustained high voltage hypersynchrony, irrespective of the nature of the seizure inducing agent used.

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Experimental Production of Seizures in the Macaque by Temporal Lobe Lesions

Julian R. Youmans, M.D.

THERE HAS BEEN considerable interest in epileptic seizures related to the temporal lobe since Jackson's[1] early description of several cases of epilepsy with dreamy states and other manifestations of temporal lobe dysfunction. An example of these was the case of a young physician with a small cavity and softening in the left uncinate area. This lesion resulted in dreamy states, smacking of the lips, and automatic movements of a profound complexity, such as seeing a patient and prescribing treatment without memory for the event. The importance of seizures originating in the temporal lobe may be seen in the electroencephalographic study of 2,300 epileptic patients by Jasper, Pertuisset, and Flanigan.[2] They found that one in every five epileptic patients has the origin of his seizure in the temporal lobe (including the insula and uncinate-hippocampal systems), and of those patients with cortical foci for seizures, one-half or more of these foci are in the temporal cortex.

Production of seizures in experimental animals has been difficult, and numerous methods[3–6] have been tried. In 1937 Sherp and Church[7] reported the development of acute convulsive seizures in rabbits and other animals following intracerebral injection of aluminum salts. Kopeloff and his group[6,8,9] used this irritant with success to produce lesions in the frontal, parietal, and occipital lobes which resulted in seizures. The present study is concerned with the production of seizures secondary to irritant lesions placed in the anterior portion of the temporal lobe. This area was chosen because of its frequent involvement in epilepsy in man.

METHODS AND PROCEDURES

Operations were performed on five monkeys (Macaca mulatta). Aseptic technic was used in all operative procedures. Anesthesia was either by intravenous or intramuscular injection of 2½ per cent sodium Penthothal or by inhalation of ether. Alumina cream (aluminum hydroxide) was prepared by autoclaving Wyeth Amphojel or the gelatinous purified aluminum hydroxide of

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This work was aided by grant 983 from the Faculty Research Fund of the Horace H. Rackham School of Graduate Studies and performed in the laboratory of comparative neurology, department of anatomy, and the central nervous system research unit of the Kresge Medical Research Laboratory, University of Michigan, under the direction of Professor Elizabeth C. Crosby.

the Fisher Scientific Company. All animals were of normal, healthy appearance and their weights ranged from four to 12 pounds.

PROTOCOLS

Protocol No. 1, Animal No. 82.

Preoperative study. This animal, a six-pound male macaque, had a normal neurologic examination and electroencephalogram. His behavior was normal during several days of observation.

Operation 1. 2-1-55. Anesthesia was obtained by intravenous and intramuscular injection of 2½ per cent sodium Pentothal. A right temporal craniotomy was performed. Without opening the dura, a No. 20 gauge needle was inserted subcortically into the tip of the right temporal lobe and 1 cc. of alumina cream (Wyeth Amphojel) was injected. The incision was closed with interrupted silk sutures. This procedure was well tolerated by the animal.

Postoperative results. The postoperative course was uneventful except for decreased activity for nine to ten days. Serial postoperative electroencephalograms revealed decreased voltage in the right temporal area for about three weeks postoperatively. The electroencephalograms done six weeks postoperatively were comparable to the normal preoperative recordings.

Operation 2. 3-21-55. This procedure was performed six weeks and six days after operation 1. Anesthesia was obtained by inhalation of ether. A procedure similar to that reported in protocol 1 was carried out and 1.2 cc. of alumina cream (Wyeth Amphojel) was injected into the same area. This procedure was tolerated well by the animal.

Postoperative results. Except for moderately decreased activity, the postoperative course was uneventful until the eighth day when the animal was found dead in his cage. He was active and appeared well when observed two hours earlier. He had lost no weight.

Postmortem examination. His mouth and oral pouches were full of food. There was saliva about the mouth and food and foam from saliva in the throat. The tongue was bitten in several places. There was questionable cyanosis of the oral membranes. The dura was greatly thickened over a 1½ cm. area of the anterior and lateral aspect of the temporal pole with a white granular exudate (figure 1) over this same area. Gross transverse sections of the brain revealed softening of the cortex and the immediately subcortical white matter of the anterior 1 cm. of the middle temporal gyrus and the anterior 1½ cm. of the inferior temporal and the hippocampal gyri. The amygdala was not involved.

Comment. The first irritative lesion produced only transient signs of a decreased activity and a depression of voltage in the right temporal area as measured by the electroencephalograph. In our opinion, the second lesion was followed by a massive grand mal seizure on the eighth postoperative day. This seizure was fatal. No electroencephalogram was taken.

Protocol No. 2, Monkey No. 97.

Preoperative study. This animal, a four-pound male macaque, had the same preoperative studies as No. 82.

Operation 1. 4-7-55. Anesthesia was obtained by inhalation of ether. A right temporal craniotomy was performed. Without opening the dura, 2 cc. of alumina cream (Wyeth Amphojel) was injected subcortically and intracortically into the anterior portion of the right temporal lobe.

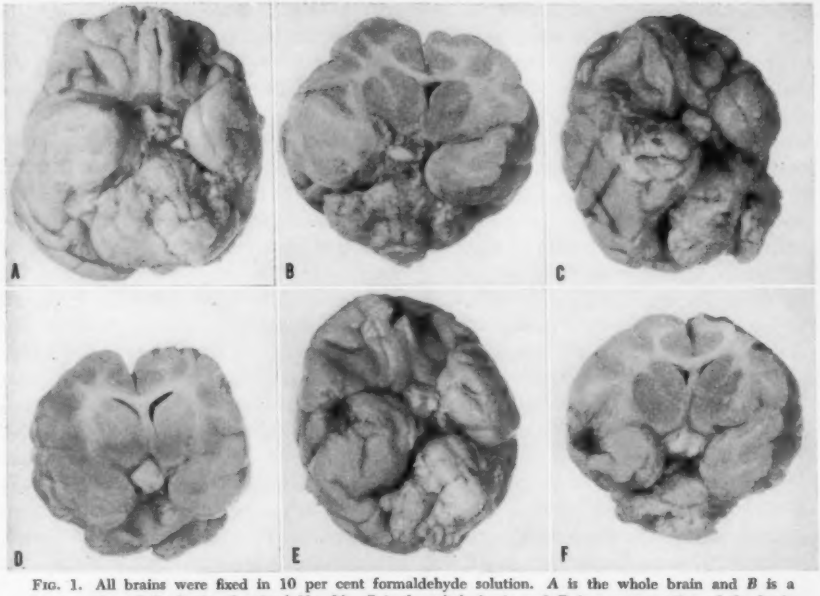

FIG. 1. All brains were fixed in 10 per cent formaldehyde solution. *A* is the whole brain and *B* is a cross section of the brain of animal No. 82. *C* is the whole brain and *D* is a cross section of the brain of animal No. 97. *E* is the whole brain and *F* is a cross section of the brain of animal No. 98. Discussion of each brain is given in the text.

Postoperative results. On the first postoperative day the animal was normal except for a slight inactivity. During the second postoperative day he held his right hand in an abnormal manner with fingers and thumb straight. There was obvious clumsiness of the right arm during walking. On examination the animal appeared normal except for a questionable weakness of the right hand, apparently due to a decrease in tone. The right hand tended to remain in the position in which it was placed, and the right arm probably was slightly resistant to passive movements. The left arm and both legs were normal. During the fourth to the sixth postoperative days he continued to exhibit awkwardness in the use of the right arm; otherwise his movements and behavior were normal. On the seventh postoperative day he had three brief seizures occurring during a two-hour period in the morning. The animal appeared normally active, then within ten to 15 seconds became apathetic. His eyes stared to the right and he had chewing movements. He moved only on severe prodding and then only a step or so to one side, as if he were maintaining his balance. These seizures occurred five to eight minutes apart and each episode lasted one to two minutes, then cleared up completely. There was no twitching of the facial muscles. He was normal during a two and a half hour observation period the same evening. On the eighth postoperative day he was described by several observers as being "dreamy and apparently out of contact with his surroundings." He be-

came active if prodded but, if undisturbed, would sit bent forward with one hand folded on the other. He appeared somewhat unsteady. During two hours of observation he had two abnormal episodes that lasted about five minutes each. During these periods his head turned to the right and his eyes deviated up toward the right. There were apparently purposeless movements of the arms and hands, which were more marked on the right. He opened his mouth, moved the lower jaw from side to side, and then closed his mouth. These jaw movements were interpreted as chewing movements. On the ninth postoperative day the animal appeared normal during eight hours of observation. An electroencephalogram revealed a depression of voltage in the temporal area similar to that seen in monkey No. 82. On the tenth postoperative day the animal was found dead in his cage.

Postmortem examination. There was food in the oral pouches and mouth, and the tongue was severely bitten. The dura was normal except for a thickening (to 1½ mm.) in a 2 cm.^{2} area over the right temporal pole. An irregular plaque of white granular exudate (figure 1) was noted in patches over this same area. Sections of the brain revealed softening of the cortex and the immediately subcortical white matter in the anterior 1½ cm. of the superior, middle, and inferior temporal gyri and the hippocampal gyrus. The amygdala was not involved in the softening process.

Comment. This animal had seizures of temporal lobe origin, with minimal impairment of consciousness and automatic movements of the arms, hands, and jaw. These were very similar to the partial seizures studied in man by Gastaut.[10] The apparent marked disturbance of proprioceptive sense seen here has not characterized the cases reported in man.

Protocol No. 3, Monkey No. 98.

Preoperative study. The studies were the same as with animal No. 97.

Operation 1. 4-7-55. Anesthesia was obtained by 2 cc. of 2½ per cent sodium Pentothal administered intramuscularly in divided doses. A right temporal craniotomy was performed, and the dura was opened so as to expose the cortex of the anterior portion of the temporal lobe. A small spatula was used to introduce 0.2 gm. of alumina cream (Fisher alumina-gel) intracortically and subcortically in the anterior tip of the temporal lobe. This material quickly dissolved in the spinal fluid present and much of it escaped. Using a 20-gauge needle, 0.5 cc. of Wyeth Amphojel was injected into the same region.

Postoperative results. From the first to the fifth postoperative day the animal was normal. On the sixth day (9:00 a.m.) when he was observed in his cage, he appeared to be using the right arm less well than the other extremities. He became active if prodded, but tended to sit quietly if left alone. Later he was observed for an hour (10:45–11:45 a.m.). During that period he had three attacks with progression of signs as follows: He would be alert and apparently normal and then have slowing of responses to stimulation and sluggishness, as described above. This was followed by tilting of the head slightly to the right side and a forward staring of the eyes. He was completely immobile except for definite twitches of the muscles of the right side of the face about the mouth at the rate of two to four per second. There was slight, if any, involvement of the muscles of the right eyelid, but none on the left side of the face or body.

The first episode lasted 40 to 50 seconds and, in about 20 minutes, was followed by a second attack which continued for one and a half to two minutes. Ten minutes later a third attack occurred and lasted for approximately 30 seconds. The monkey was sluggish during the interval between the first and the second attack, but apparently was normal in the interval between the second and the third episodes. The cage door was opened during the second seizure, but, although the monkey was prodded, he did not move. He awoke and ran out into the room and had to be chased back into the cage. Neurologic examination of the animal was normal despite the appearance of a slight dysfunction of the right arm. During the afternoon (5 p.m.), he appeared to be in contact with and responsive to his surroundings. His movements were slow but otherwise normal, except for a continued clumsiness of the right arm. During the morning of the seventh postoperative day he was observed at several intervals and appeared more active than the preceding day but was still sluggish and weak. No muscle twitches were noted. During the evening he was observed for one hour (8:30–9:30 p.m.). There was one questionable lapse of activity for 15 to 25 seconds, with chewing movements and several twitches of the lips toward the right. This cleared quickly. During two hours of observation on the eighth postoperative day and intermittent observation for six hours during the ninth postoperative day and night, no seizures were seen. On the morning of the tenth postoperative day he was found dead in his cage.

Postmortem examination. The oral pouches and mouth contained freshly eaten food. His tongue was bitten in several places. The old operative defect of the dura was scarred down to the cortex over the anterior and inferior region of the middle temporal gyrus on the right where a large clot of blood was noted (figure 1). Several small areas at the tip of the lobe, including the anterior portion of the superior, middle, and inferior temporal gyri and the hippocampal gyrus, were covered with white plaques of granular exudate. The cortex and the immediately subjacent white matter of the anterior portion of the superior, middle, and inferior temporal gyri were involved in a softening process. The amygdala was not included in this lesion.

Comment. Following an irritating lesion in the anterior portion of the right temporal lobe, this animal showed seizures consistent with those seen in temporal lobe epilepsy of man. In addition, he had ipsilateral facial movements on the right.

Protocols No. 4 and 5,
Monkeys No. 78 and 86.

Preoperative studies. These animals weighed eight and 12 pounds, respectively. Otherwise their preoperative studies were the same as animal No. 82.

Operation 1. No. 86 on 2-15-55 and No. 78 on 4-25-55. Anesthesia was obtained by inhalation of ether in each case. Craniotomies were performed as described above. Animal No. 78 had 0.7 cc. and animal No. 86 had 0.2 cc. of alumina cream (Wyeth Amphojel) injected into the tip of the temporal lobe in the same manner as described for animal No. 97.

Postoperative results. These animals were observed for three months and six months, respectively, without any clinical evidence of effect from the irritating lesions. The electroencephalographic

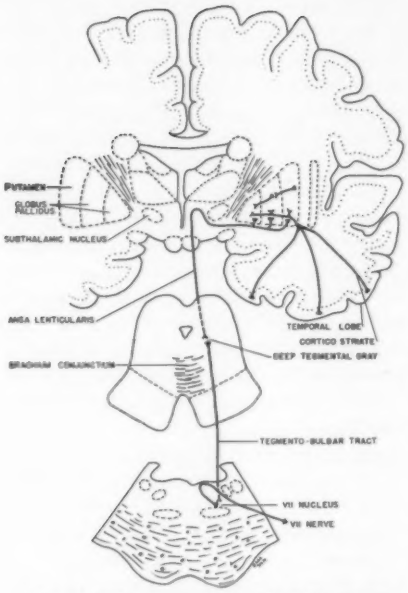

FIG. 2. This diagram shows part of the extrapyramidal connections from the temporal cortex to the bulbar nucleus of VII. The facial movements resulting from electrical stimulation of ipsilateral temporal cortex probably result from transmission of the impulses over this system.

studies of each animal revealed a depression of voltage in the operated areas; the voltage gradually returned to normal over a period of three weeks.

Comment. It is probable that the small amounts of irritating substance injected into the temporal lobe of these animals were absorbed and healing took place without sufficient scar formation to provoke seizures. This may be likened to the many traumatic lesions of the brain sustained by man which heal without any untoward symptoms.

DISCUSSION

Animal 82 had a grand mal seizure terminating in death. Whether or not this was preceded by a temporal lobe seizure could not be ascertained. Animals 97 and 98 were observed during temporal lobe seizures comparable to those seen in man. In all probability these temporal lobe seizures result from irritation of like temporal areas of the brain in monkey and man.

The jacksonian type of focal twitches of the face of animal 98 are interesting as they are due to an ipsilateral temporal lobe lesion and are movements from a "second" (or additional) motor area, such as that described by Schneider and Crosby in 1954.[11] The pathway for the discharge resulting in these movements is probably through the extrapyramidal system. The fiber tracts involved are thought to be successively: the corticostriate path, from temporal cortex to the striatum; the ansa lenticularis, from the striatum to tegmental gray; and tegmentobulbar discharge systems, from the tegmentum to the nucleus of the facial nerve. A diagram of these fiber tracts is shown in figure 2. When the middle temporal gyrus is stimulated electrically near the pole, facial movements are obtained as shown in figure 3. Placement of an irritating lesion with alumina cream in this area (as was done in animal 98) resulted in seizures in which facial movements of lesser magnitude – but strikingly similar in composition to those obtained with the electrical stimulation of the cortex – appeared. There is a possibility that the facial and chewing movements seen with temporal lobe lesions in man are a manifestation of irritation in the second motor area of this region.

Each of these animals had fresh food in his mouth and oral pouches at the time of death, and all findings post mortem were consistent with his having been eating at the time of the onset of

FIG. 3. The animal is under ether anesthesia. The photo *A* is immediately before and *B* during electrical stimulation with a silver tip electrode of the right middle temporal gyrus near its anterior pole. Factors were: 4 volts, frequency 40 per sec., and pulse duration 5 msec.

his presumably massive and fatal seizure. The temporal "second" motor area subserves the movements of the face and upper extremity used in eating, hence it is also a secondary correlation area for this activity. The question arises as to the relation, if any, of these functions and the triggering of seizures in these animals by the afferent impulses set up from the face and upper extremity by the process of eating. To the author, this would seem to be a likely possibility. The afferent impulses from the eating movements (from face, arm, and hand in the monkey) are projected to this "second" motor area and other cortical areas. Under normal circumstances, this extrapyramidal arc is correlated with the pyramidal arc through the striatum and other centers so as to modify and regulate the general and associated movements which are automatic in the feeding process. When an irritating or stimulative lesion is placed in this arc, the afferent impulses may be modified to set up a reverberation of impulses leading to a convulsive seizure.

The apparent lack of positional sense in the right arm and the decreased use of the right arm and hand in animals 97 and 98 are difficult to interpret. In each case the unsteady movements of the arm in locomotion and the animal's preference for the use of the left arm and hand suggest that he may have had an apraxia of the right arm and hand. In the literature apraxia is ascribed to lesions of the frontal, parietal, and occipital lobes, but the writer has found no mention of such apraxia in temporal lobe lesions. This finding may result from an alteration of the normal checks and balances of the pyramidal system and the extrapyramidal system caused by a stimulatory lesion in the latter.

The electroencephalographic findings of decreased voltage in the temporal area on the operated side are consistent with those ordinarily seen after the trauma of surgery. Unfortunately, the abnormal behavior or movements occurred at times other than during the electroencephalographic recordings. Discrete areas of suppressor responses from

electrical or strychnine stimulation of the temporal cortex have been described by Huertas, O'Doherty, and Forster.[12] These areas are grouped in the first temporal convolution near the base of the Sylvian fissure. All recordings of the present experiments were done through scalp leads. In each instance, the low voltages were recorded with the temporal and midtemporal leads. This depression was a constant feature of any particular recording and was not accompanied by clinical signs. Hence, these findings do not appear to be comparable to those of Huertas and co-workers.[12]

Klüver and Bucy[13–16] obtained psychic blindness, oral tendencies, "hypermetamorphosis," hypersexuality, emotional changes, and change in dietary habits following bilateral ablation of large areas of the anterior temporal lobes. The animals reported on in the present experiments showed none of these effects except the emotional changes as represented by moderate apathy. This apathy may represent a lesser component of the marked emotional changes noted by Klüver and Bucy and also by Poirier.[17] However, one must remember that the lesions reported in this paper were irritative, while the former were destructive.

SUMMARY

Irritating lesions were created by placing alumina cream in the temporal lobes of five monkeys. Observations of temporal lobe seizures and evidence for grand mal seizures in three of these animals are given. A discussion of these findings and some of their implications are presented.

The author wishes to express his deep appreciation to Dr. Basu K. Bagchi and Miss Hazel Calhoun, section of electroencephalography, department of psychiatry, University of Michigan, for their help in recording and interpreting the electroencephalographic studies.

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Hereditary Cerebellar Ataxia

Olivopontocerebellar Type

Joseph H. Chandler, M.D. and Jose Bebin, M.D., Ph.D.*

CLASSIFICATION of the inherited ataxias is one of the most controversial and perplexing problems in neurology. The current trend is to regard them as a spectrum of closely interrelated diseases,[1,2] as evidenced by the classification of the spinocerebellar degenerations suggested by Greenfield in his recent survey.[2] At one extreme are the predominantly spinal forms such as Friedreich's ataxia, Roussy-Levy syndrome, Charcot-Marie-Tooth disease, and familial spastic ataxia. At the other extreme are the predominantly cerebellar forms such as the olivocerebellar atrophy of Holmes and the olivopontocerebellar atrophy of Dejerine and Thomas. The intervening group has varying mixtures of spinal and cerebellar involvement. Menzel's family with pathologically demonstrated olivopontocerebellar atrophy plus corticospinal, posterior column, and spinocerebellar atrophy in the cord is the prototype of this transitional group. Overlapping and shading within the spectrum is demonstrated by the Schut[3] family with its four basic types, of which one resembles Friedreich's ataxia, another has spastic paraplegia and minimal ataxia, a third shows cerebellar and corticospinal involvement, and a fourth has predominantly cerebellar manifestations.

Dejerine and Thomas[4] in 1900 described an ataxia which came on in middle age and clinically manifested itself by progressively unsteady gait, dysarthria, incoordination of the hands, and absence of spinal cord signs. They were unable to establish an hereditary or familial tendency in the two cases studied. On the basis of the neuropathologic findings they named this entity olivopontocerebellar atrophy. An inherited form of this same disorder has been reported by a few observers.[3,5,6] Greenfield[2] considers the typical pathologic findings in olivopontocerebellar atrophy to be shrinkage of the ventral half of the pons, disappearance of the olivary prominences of the medulla, and reduction in the size of the cerebellum. Histologic findings include loss of the nuclei pontis, sclerosis and marked loss of cells throughout the inferior olives, demyel-

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ination of the middle cerebellar peduncles, and varying amounts of atrophy of the cerebellar cortex.

CLINICAL MATERIAL

Recently seven affected members in a family with an inherited ataxia have been studied. Three of these were examined by the authors, two had previously been studied at University Hospital, and two had been patients in the state mental hospital (table 1).

The clinical findings in all seven cases were strikingly similar. An ataxic gait, incoordination of the hands, rest tremors of the head and upper extremities, tremor of the tongue, and mental deterioration were found in all of them. There was no evidence of spinal cord involvement by neurologic examination; nystagmus, optic atrophy, and pes cavus deformity of the feet were uniformly absent. The age of onset of the disorder ranged from 31 to 44 years; there was variation in sequence of appearance and the rate of progression of symptoms.

The pedigree was investigated at the heredity clinic of University Hospital (figure 1). The taint appears to be inherited as a simple mendelian dominant. The central nervous system of case II-3 was available for neuropathologic study.

CASE REPORTS

III-1. J. O., the propositus, was first examined at 46 years of age, two years after the onset of his illness which began with unsteadiness of gait. This was soon followed by impairment of skilled hand movements and difficulty in speaking. He became irritable, forgetful, and was easily upset.

Initial physical examination on October 2, 1950 revealed an elderly appearing white man who showed poor calculation, impairment of

TABLE 1
CHART OF CLINICAL FINDINGS

Pedigree		*Age*	*Sex*	*Age at Onset*	*Age at Death*	*Signs*	
III-1	J. O.	50	Male	44	–	Dementia, dysarthria, facial grimacing, right facial weakness, ataxic gait, incoordination of hands, tongue tremor.	Intellectual deterioration. EEG. 5½–6½ sec./low voltage in motor and premotor areas. X-ray skull and chest neg. Urine neg. CBC neg. Kahn neg.
III-2	M. O. H.	54	Female	33(?)	–	Dementia, rest tremors of head, tongue and arm, decorticate posture, truncal ataxia, facial grimacing, diminished ankle jerks.	——
III-3	G. O.	35	Male	31	35 (suicide)	Intellectual loss, psychosis, facial grimacing, tremor of tongue, ataxia and dysdiadokokinesis of upper extremities, staggering gait.	I.Q. 71. Intellectual deterioration. EEG. consistent with diffuse brain damage. X-rays skull neg. Lumbar puncture Kahn neg. T.P. 68 mg.%, cells 0. Urine neg. CBC neg.
II-3	J. C.	58	Male	45	60	Dementia, unreactive pupils, rest tremor of tongue and upper extremities, dysarthria. Incoordination of hands, ataxic gait.	Urine neg. CBC neg. Kahn neg.
II-4	M. C. C.	49	Female	45	63	Dementia, psychosis, perioral tremor, tremor of hands, dysarthria, dysdiadokokinesis, peculiar gait.	——
II-6	M. C. K.	57	Female	42	–	Intellectual loss, rest tremor of head, tongue and hands, ataxic gait, dysdiadokokinesis.	——
I-2	M. B. C.	30	Female	30	(?)	Psychosis, intellectual loss, difficulty walking, unsteadiness of hands, bedridden.	——

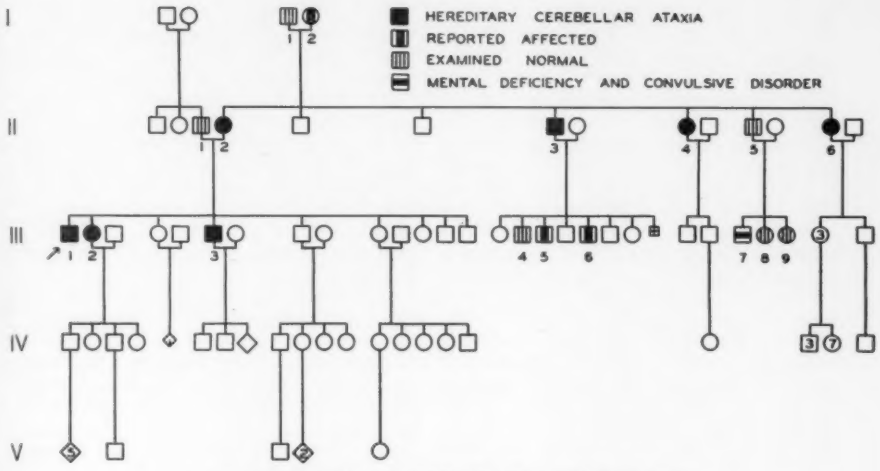

FIG. 1. Pedigree of family exhibiting hereditary cerebellar ataxia.

memory and judgment, and a silly euphoric affect. Facial grimacing and slight paralysis of the face were observed; speech was dysarthric. The general muscle bulk was diminished. Gait was shuffling and unsteady with a widened base, but there was no Romberg sign. Dysdiadokokinesis was found and the rebound phenomenon was elicited. All sensory modalities were intact.

Chest and skull roentgenograms were negative; spine films showed a spondylolisthesis. Psychometric testing disclosed mental deficiency, but there was also evidence of intellectual deterioration. An electroencephalogram was interpreted as consistent with diffuse brain damage.

The patient was reexamined four years later. History at this time revealed that he had had frequent temper outbursts, had been physically assaultive, and was unable to care for his personal needs. He was found to be disoriented and to have severe impairment of intellectual functions. No nystagmus was elicited. There was a rapid, rhythmic tremor of the right lower half of the face and a fine, rhythmic 4 to 6 per second tremor of the tongue. Speech was indistinct and muffled. Muscle bulk was generally diminished, but there was no alteration of tone on passive movement. There were occasional purposeless twitching movements of the fingers, hands, head, and neck. There was drifting of the right arm downward and of the left arm upward, with hyperextension and "piano playing" movement of the fingers. On finger-to-nose test there was marked past pointing with a wide excursion and a rhythmic 2 to 3 per second side-to-side tremor. The heel-to-shin test was done with difficulty because of tremor and ataxia. On rapid alternating movements of the wrists there was gross adiodokokinesis. Rebound phenomenon was easily elicited. He was unable to walk without support. His gait was wide-based and unsteady, and the feet were placed uncertainly with gross tremor. Sucking and grasp reflexes were observed, but the deep reflexes were normal. There was no sensory impairment. There was a mild dorsal kyphosis, but no pes cavus.

III-2. M. O. H. was examined on August 21, 1954 at the age of 54 years. She had been noted to have unsteadiness of gait in her early thirties. Her walking became severely disturbed and she would stumble and lurch about the house, holding onto furniture for support. Her speech became slurred and "words would run together." Within two years after onset there appeared trembling and shaking in the hips and legs and jerking "wild" movements of the arms. Since the onset of her illness there has been progressive failure of memory, faulty idea-

tion, and episodes of agitation and combativeness. For the past five years the patient was observed to have visual and auditory hallucinations. She had been bedridden for four years.

The patient showed a general wasting, incontinence, and severe dementia. Except for an occasional isolated word, she was unable to communicate. Her position was one of flexion of the joints of the upper extremities, with radial deviation at the wrist joints. The lower extremities were in extension, with some inward rotation at the hip joints. There was a 2 to 3 per second tremor of short arc which involved the forearms and hands and a fine rhythmic flexion-extension tremor at wrists and fingers. When the patient was supported in the sitting position there was side-to-side swaying of trunk; the upper extremities waved arrhythmically and stiffly from side to side. Movements were wavering, unsteady, and too poorly organized to accomplish an effective act. There was a variable plastic resistance to passive movement. There were nonrhythmic repetitive movements at the corners of the mouth, with an occasional grimace. There was no nystagmus and no apparent loss of visual acuity. There was a 4 to 6 per second rhythmic rest tremor of the tongue. She reacted to pinprick, deep pressure, and vibration when applied to face, trunk, and extremities by clumsy attempts at withdrawal and wild swinging movements of the arms. Grasp and sucking reflexes were elicited. Deep reflexes were normal, aside from achilles reflexes which were absent. No scoliosis or pes cavus deformity were observed.

III-3. G. O. was examined on April 2, 1941 at the age of 35 years. Four years before admission he was observed to have difficulty controlling his legs; steps became hesitant and unsteady and gait became progressively more clumsy and staggering. During the year prior to admission he had difficulty holding and manipulating tools at work. There had been a marked personality change for several months; he frequently threatened his wife and children with bodily harm, became easily upset, and had failure of memory.

Examination showed a low intellectual level consistent with feeblemindedness or mental deterioration, occasional tremor of head and neck, and twitching and grimacing movements of perioral muscles. No nystagmus was seen. There was tremor of the tongue. Speech was monosyllabic. There was abnormal spreading of the fingers, with irregular ataxic and tremor-like movements. Muscle tone and power were normal. Finger-to-nose test showed ataxia bilaterally with terminal gross oscillatory tremor. There was no definite spontaneous past-pointing. Musculature of lower extremities showed no loss of bulk, power, or tone. There was moderate static and considerable kinetic ataxia on the heel-to-knee test. All reflexes were normal. Sensory changes were absent. Station was slightly unsteady, and the Romberg sign was suggestively positive. The gait was broad-based and ataxic.

Skull roentgenograms were normal, as was spinal fluid examination. The intelligence quotient was 71; the presence of an average vocabulary suggested that intelligence had once been approximately normal. The electroencephalogram showed evidence of diffuse brain damage.

The patient was transferred to a state hospital where he committed suicide on July 12, 1941.

II-2. K. M. C. began to show physical deterioration and jerking movements in her early thirties. She lost control of her voice, legs, and hips. By age 42 she could no longer climb stairs. No mental deterioration was noticed. Prior to death at the age of 49 her legs were said to have become stiffened.

II-3. J. C. first had grand mal convulsions at the age of 30. At 45 years he began to be irritable and disagreeable, speech became muffled, and his walking was clumsy. A few years later he began to express paranoid ideas, became physically abusive, and had visual hallucinations and memory loss. He became unable to walk without help. He was unable to feed or dress himself. He was admitted to Traverse City State Hospital on August 7, 1941 at the age of 58.

On examination his comprehension was poor, attention span diminished, stream of thought slow and disconnected, and memory markedly impaired. He was unable to perform simple calculations and was disoriented in all three fields. The pupils did not react to light, the pharyngeal reflex was absent, he had difficulty with phonation, and speech was thick. There was tremor of the tongue. There was generalized muscle weakness, with tremor of the upper extremities and ataxic gait. He died of bronchopneumonia on March 10, 1943. His brain was available for neuropathologic study.

II-4. M. C. C. lost interest in her family at the age of 45. She developed delusions and paranoid ideas and became depressed and unable to concentrate. Her judgment was severely impaired and she threatened suicide.

Examination revealed that she was fearful and suspicious, with many delusions and visual hallucinations. Her memory was fair for past events and poor for recent events. There was a tremor of the muscles about her mouth and nose, as well as of the extended hands and fingers. Speech was defective. Her reflexes were sluggish. Two months after admission a peculiar choreic gait was noted.

Two years later she was noted to have a peculiar gait and lack of coordination of hands. The head and arms were in continual activity and her mouth twitched. Some passive resistance to movement was noted. She talked gibberish and was completely inaccessible mentally. She died of infection at age 63.

II-6. M. C. K. was first noted to exhibit progressive physical and mental changes when about 42 years of age. At age 45 her hands and arms began to tremble; she became clumsy in the use of her hands and often dropped things. At the same time her gait became unsteady and swaying; she would trip over her feet and lose her balance and fall. Over the next ten years she had become increasingly careless about her personal appearance, exhibited intellectual loss, and suffered from periods of depression, moodiness, and agitation.

On examination her recent, remote, and retentive memory were moderately impaired; her fund of knowledge was limited. There was a 4 to 6 per second rest tremor of the tongue. There was no muscular weakness or wasting and no alteration of tone or increased resistance to passive movement. There was a fine rhythmic affirmative 4 to 6 per second tremor of the head and a flexion-extension tremor of fingers and wrists. Amplitude of tremor was accentuated by movement and change in position. It could not be arrested voluntarily. Finger-to-nose test was performed without past-pointing, but with considerable accentuation of the amplitude of the tremor. There was disorganization of rapid alternating movements at the wrists. Heel-to-shin test was performed with side-to-side tremor and interruptions of smoothness of the movement. Her gait was wide-based; feet were placed slowly and uncertainly. The Romberg sign was negative. Sensory examination was normal, as were the reflexes. There was no scoliosis or pes cavus.

I-2. M. B. C. developed episodes of crying, melancholia, and irritability at the age of 30 and was admitted to Traverse City State Hospital. On physical examination her mental action was slow and memory was fair; she had illusions and hallucinations. At discharge it was noted that her mind reacted feebly and imperfectly and that she was unable to connect any idea.

Her family reported that she later developed difficulty walking and unsteadiness of hands and became bedridden.

PATHOLOGIC FINDINGS (Case II-3)

The body was emaciated and dehydrated. The left lung showed a bronchopneumonic consolidation of its lower lobe with occlusion of the main bronchus by a thick purulent exudate. There was chronic heart disease with sclerosis of the mitral valve and atherosclerosis of the coronary arteries and aorta. The liver showed chronic passive congestion and a nutmeg appearance. The spleen was markedly congested, as was the pancreas.

Examination of the brain showed moderate thickening of the inner meninges and moderate generalized atrophy of the cerebrum. The brainstem and cerebellum weighed 100 gm. and were markedly atrophic in contrast to the cerebrum (figure 2). The cerebellar atrophy was diffuse and affected equally the hemispheres and superior vermis; there was better preservation of the inferior vermis and flocculus. On section there was marked degeneration of the cerebellar folia. The atrophy in the brainstem affected mainly the basilar portion of the pons, where the pontocerebellar fibers appeared greatly degenerated while the corticospinal tracts appeared intact. The inferior olives were markedly atrophic. Cross sections of the brain showed moderate atrophy of the cortex and normal

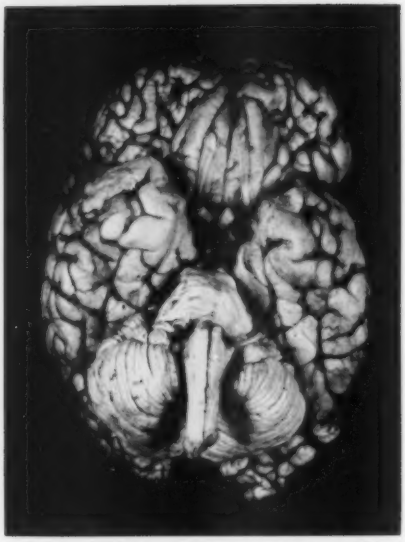

FIG. 2. Gross view of brain showing the atrophy of the cerebellum, pontile basis, and inferior olives.

gross appearance of the basal ganglia and thalamus.

Histologic examination

Spinal cord.—Only the upper segments of the spinal cord were available. The leptomeninges were slightly thickened. Sections stained with Nissl showed a normal appearance of the gray and white substance. The sections stained by the Weigert method showed pallor of the olivospinal and spinocerebellar tracts and to a much lesser degree the fasciculi gracilis.

Medulla.—Nissl sections of different levels of the medulla oblongata showed moderate thickening and fibroblastic changes of the leptomeninges. In the arcuate nucleus there was almost a complete loss of ganglion cells; the few that remained were shrunken and pyknotic. The chief olivary nucleus and ventral and dorsal accessory olivary nuclei showed marked cellular reduction with considerable gliosis. The nuclei of the cranial nerves and the central and lateral reticular gray areas appeared normal. The preparations stained by the Weigert technic showed marked reduction of the olivocerebellar fibers (figures 3 and 4). The ventral external arcuate fibers were diminished in number. The inferior cerebellar peduncle showed a reduction in the number of its fibers. The corticospinal system, the medial lemniscus, the central tegmental bundle, and the medial longitudinal fasciculi appeared normal. The dorsal spinocerebellar tracts appeared paler than normal.

Pons.—Nissl preparations of the pons showed moderate thickening of the leptomeninges and some arteriosclerotic changes in the basilar artery. The gray nuclei at lower and upper levels showed almost normal appearance in number of cells, but at the middle level there was loss of cells with degenerative changes of many of them. The superior olives and the nuclei of the tegmentum of the pons showed no pathologic changes. Weigert sections of the middle portion of the pons showed a marked demyelination of the pontocerebellar fibers and of the middle cerebellar peduncles (figure 4). The ventral and dorsal strata of the pons appeared to contain normal myelin. Similar normal appearance was observed in sections made from lower and upper pontine levels. The corticospinal system, the sensory systems, the central tegmental bundles, and the superior cerebellar peduncles appeared normal.

Cerebellum.—Sections of the cerebellar hemispheres and vermis, including the dentate nuclei, stained by the Nissl technic, showed marked atrophy of the foliae. This atrophy was diffuse and extended throughout the entire cerebel-

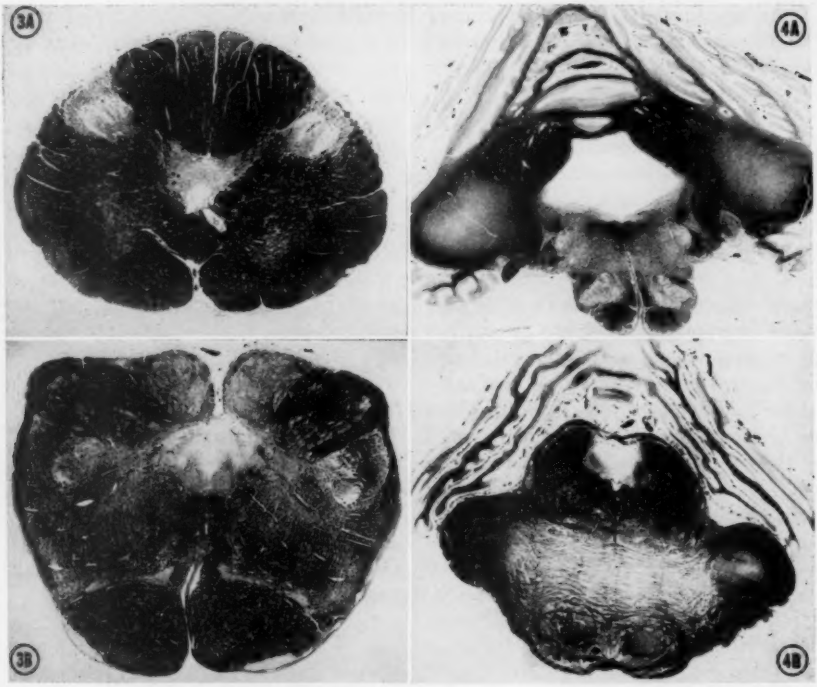

FIG. 3. *A.* Section of the medulla oblongata at the level of the decussation of the pyramids, showing mild demyelination of the ventral and dorsal spinocerebellar tracts and pallor of the dorsal portion of the fasciculus gracilis. Weigert's stain. *B.* Section of the medulla oblongata through its lower third, showing a mild degeneration of the ventral and dorsal spinocerebellar tracts. Weigert's stain.

FIG. 4. *A.* Section of the medulla oblongata through its upper third, showing a degeneration of the inferior olive, olivocerebellar fibers, and partial degeneration of the restiforme body and brachium pontis. Weigert's stain. *B.* Section of the pons through its lower third, showing marked degeneration of the pontocerebellar fibers and brachium pontis. The brachium conjunctivum, pyramids, and other pathways are normal. Marked atrophy of the cerebellar folia. Weigert's stain.

lum. There was almost a complete disappearance of the Purkinje cell layer and considerable diminution of the elements of the molecular and granular layers. In the former there was an increase of glial nuclei, and in the latter very marked reduction of granule cells. Higher magnification showed that the Purkinje, granular, and stellate cells were accompanied by gliosis visible principally in the molecular layer. No inflammatory changes were noted in the cerebellar cortex or its surrounding meninges. The dentate nuclei, at lower and higher magnifications, appeared to have a normal number of cellular elements; however, some of them showed mild chronic degenerative changes and increased amount of lipofuchsin pigment in the cytoplasm. Weigert preparations showed also marked atrophy of almost all folia of the cerebellar cortex and diffuse demyelination of the axis of the folia, with decrease in the number of myelinated fibers except

in the flocculus and rostral portion of the inferior vermis. This did not extend beyond the folia into the white matter of the cerebellar hemisphere. The capsule of the dentate nuclei as well as its hilus appeared normally myelinated. Sections stained by the silver carbonate technic (Hortega) showed complete loss of Purkinje cells and great loss of granular cells in the cerebellar cortex (figure 5A). In the molecular layer there were numerous basket cells with their axis cylinders running parallel to the surface of the laminae and their collaterals forming empty baskets about the absent body of the Purkinje cells. The climbing fibers were scanty and the mossy fibers as well as the granule cells of the granular layer were markedly diminished in number.

Midbrain.—Sections of the midbrain stained by the Nissl and Weigert technics showed a normal appearance of nuclei, including the red nuclei and substantia nigra. The corticopontine tracts, corticospinal tracts, and the superior cerebellar peduncle appeared normal.

Thalamus. The dorsal and ventral thalamus showed normal configuration and cytoarchitecture. Except for a few small areas of perivascular cuffing by mononuclear cells, no pathologic changes are present.

Basal ganglia.—The caudate nuclei and putamen appeared reduced in size. This reduction was more evident in the head of the caudate nuclei. Nissl preparations revealed decrease in number of ganglion cells in both caudate nuclei and putamen, with increase in glial nuclei. This gliosis was more intense in the subependymal areas, and it was accompanied by mild chronic ependymitis. The small arterioles of the putamen showed marked deposits of calcium in the vascular tunics. The pallidum showed mild loss of the large neurons and moderate gliosis. Weigert preparations showed normal myelin stain of the basal ganglia and internal capsule.

Cerebral cortex.—In Nissl preparations the leptomeninges of the cerebrum showed some thickening and fibroblastic

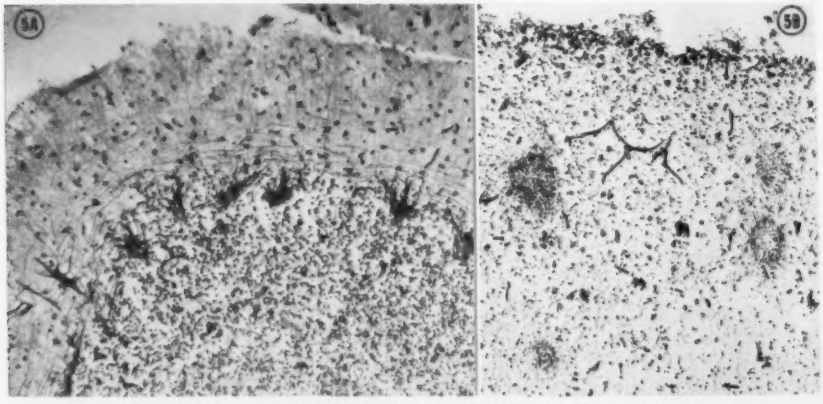

FIG. 5. *A.* Section of the cerebellar cortex showing complete loss of Purkinje cells and diminution of granular cells. The empty baskets of the stellate cells and the parallel fibers are more or less preserved. Silver carbonate stain of Hortega. *B.* Section of the temporal lobe cortex showing marked atrophy with loss of neurons and presence of numerous senile plaques. Silver carbonate stain of Hortega.

changes. Some of the small vessels had calcium deposits in their tunica media, with moderate arteriosclerotic changes. There was moderate loss of ganglion cells of the cerebral cortex, with increase of glial nuclei throughout but preservation of normal cytoarchitecture. Some of the neurons showed mild chronic degenerative changes. These changes were marked in the temporal region, where there was greatest loss of ganglion cells and an increase of glial elements. Numerous senile plaques were observed Hortega silver staining technic (figure 5B).

CONCLUSIONS

Examples of olivopontocerebellar atrophy with pathologic findings limited to medullary olives, pons, and cerebellum are rare. Even Dejerine and Thomas,[4] in their original description, found some symmetric degeneration in the anterior and lateral margins of the higher cervical segments of the spinal cord. More commonly there is also involvement of one or more of the long tracts of the spinal cord, such as dorsal columns, corticospinal tracts, and dorsal and ventral spinocerebellar tracts. Occasionally motor nuclei or cranial nerves and anterior horn cells of the spinal cord are involved.[3,7,9]

Ley,[10] Rosenhagen,[6] and Aring[11] have pointed out the occurrence of extrapyramidal tremors, rigidity, and abnormal involuntary movements associated with olivopontocerebellar ataxia, which they have ascribed to gliosis and cell loss in the basal ganglia and substantia nigra.

There is a definite tendency for varying degrees of mental deterioration to appear in the later stages of the disease. Mental symptoms occur more commonly in cases which run a subacute course.[2] The high incidence and relatively early appearance of intellectual loss and psychosis found in this report is rather unusual. The presence of numerous senile plaques throughout the cerebral cortex is an interesting finding that is difficult to interpret.

SUMMARY

Seven cases of a dominantly inherited cerebellar ataxia with onset in third and fourth decades are reported. Clinical findings are strikingly uniform. Neuropathologic observations in one case resemble those of olivopontocerebellar atrophy.

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Observations on the Pain and Trigger Mechanism in Trigeminal Neuralgia

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IN THIS REPORT the term trigeminal neuralgia refers specifically to the syndrome of tic douloureux. To be considered tic douloureux, each case presented the triad of paroxysmal attacks of pain, pain limited to the distribution of the trigeminal nerve, and induction of the pain by stimuli to sensory endings in the trigeminal area.

This syndrome has been recognized for centuries. In 1821 Bell of England and Magendie of France showed that the trigeminal, and not the facial, was the sensory nerve of the face.

In 1901 Frazier, following the suggestion of Spiller, developed the subtemporal craniotomy using the extradural approach for a retroGasserian subtotal rhizotomy. Frazier went on to perform this operation on over 700 cases, with a mortality of less than one-half of one per cent.[1] In 1925 Dandy presented his posterior fossa approach, which was very successful in his cases. In his large series of over 500 cases[2] he was able to explore the cerebellopontine angle and gain an experience which has been unequaled.[3]

In 1938 Sjoqvist presented his excellent study on section of the bulbospinal tract of the fifth nerve.[4] This type of operative procedure must, of course, remain a formidable one, and the search for a safer, simpler, and more effective operative technic has continued. Especially to be desired would be an effective method which would not subject the patient to postoperative trigeminal anesthesia.

PERIPHERAL DECOMPRESSION

In 1951 Woltman suggested to Shelden the possibility of decompression of the trigeminal nerve in tic douloureux after a decompression of the seventh nerve in a case of facial tic.[5] From 1951 to 1953 ten patients with third or second division tic had a decompression procedure carried out at the foramen rotundum or ovale with a neurolysis of the nerve involved. The immediate results were good. There was cessation of the pain, with only a minimal hypalgesia and no operative morbidity.

During this period it was learned that Taarnhoj was obtaining similar results in Copenhagen by decompressing the posterior root. Following Taarnhoj's publication in 1952,[6] some observers ap-

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peared to conclude that, since decompression helped, then compression might be the causative factor in trigeminal neuralgia. However, if relief of pain in tic douloureux could be obtained either by decompression of the posterior root or the peripheral branches, the two methods must have something in common. The one common feature appeared to be the operative trauma. Postoperative hypalgesia, even if only temporary, was also reported after posterior root decompression, but was apparently not considered significant.

In more anterior peripheral decompression, as the technic of handling the high-speed dental drill around the foramina improved, the trauma to the nerve and the postoperative hypalgesia decreased. Of the ten patients operated upon, five had a recurrence of symptoms. The other five have remained free of recurrence from two to four years.

POSTERIOR ROOT COMPRESSION

It was considered that the trauma of surgery rather than the decompression may have been the curative factor in both so-called "decompression" procedures. It was decided to try merely compressing the trigeminal nerve. On theoretical grounds for a possibly more lasting result, it was done with a retroGasserian approach (figure 1). The first compression procedure was done in December 1953. To date 28 compressions have been done. The results have been most gratifying. There has been no failure of pain relief, and thus far (up to 15 months) no recurrence. There has also been no mortality or surgical morbidity. There have been no cases of postoperative facial palsy, extraocular weakness, corneal disturbance, or fifth motor involvement.

FIG. 1. Technic of posterior root compression. A blunt dissector is used to compress the lower half of the root after opening the dura propria with a right-angled knife.

Although there has been no exact way of measuring the amount of compression used, in general less and less pressure has been applied at each operation. An attempt has been made to compress selectively only those fibers coming from the division involved. This has been done to try to determine the smallest amount of pressure needed to effectively stop the pain, and thus give a minimal amount of postoperative hypalgesia. On several of the recent compression procedures the dura was not even opened, the fibers being compressed without being directly exposed. Three of the most recent patients have all had a few tic pains immediately postoperatively, but these subsided spontaneously in one to three days without reoperation. Whether this type of light compression will have a lasting effect is, of course, not yet known. Such attempts are felt justified because reoperation for further compres-

sion is felt to be superior to rhizotomy with a permanent anesthesia. It is still to be hoped that in the future some safe and effective medical treatment may find these patients with the root still intact should they develop a recurrence of pain.

CERVICAL NERVE BLOCK

We did not, and still do not, have a good explanation for the results of this compression procedure. The fact remains that it works, and there must be a reason. Further investigation certainly seemed indicated. In early 1954, soon after the first compression procedure, the authors became acquainted with the papers by Wyburn-Mason[7,8] in which alcohol block or section of the greater auricular nerve in the treatment of tic douloureux was described. Wyburn-Mason listed 13 different reasons for considering tic douloureux to be an involvement of the high cervical nerves rather than the trigeminal nerve. Although some of his conclusions did not seem warranted to the present authors, he did give the impressive number of 56 cases of tic cured by this procedure as long as the trigeminal pain had not involved the tongue.

We have all seen cases of high cervical injury, such as those due to whiplash, where there are objective sensory changes well up into the face in the area considered to be trigeminal. Consequently it was felt that this line of approach certainly deserved further investigation. As a first trial, a 63 year old female patient with typical third division tic had her greater auricular nerve blocked with xylocaine in February 1954. This gave complete relief of spontaneous pain and abolition of the trigger zone of her lower lip. After the anesthesia wore off, her pain returned unchanged. Then the greater auricular nerve was sectioned in the neck and she has had complete relief to the present time (12 months). It was, of course, hoped that this simple procedure would be a uniformly effective tool in the neurosurgeon's armamentarium. However, this has not proved to be so in our hands. While the results have been dramatic at times, and the importance of this procedure in attempting to further our knowledge of the mechanisms in this disease cannot be over-emphasized, the relief obtained in many instances has not been as great as had been hoped.

The procedure of block and even of section of the greater auricular nerve is so simple that on occasion it has been done as an outpatient procedure. Xylocaine block has been done on over 30 cases with trigeminal pain in various combinations in all three divisions, with and without pain in the tongue. Of these patients, 11 experienced complete or almost complete relief from tic pain and surgical section or crushing of the greater auricular nerve was done. In five this has proved to be adequate, but five others had a recurrence and a trigeminal compression was done. In the eleventh and most recent case, there was also failure of pain relief and a further step is contemplated.

Before describing results from the greater auricular nerve blocks further, it is necessary to discuss the next step in our investigation of the pain and trigger mechanism, namely, the use of nerve blocks of the greater occipital nerve. It was felt in the light of the results from trigeminal compression and from the results in our initial greater auricular nerve section, that the interruption of sensory stimuli into the central connec-

tions of the upper cervical cord might in some way play a role in the cessation of tic pain. Consequently the greater occipital nerve was thought of at once. The greater auricular nerve is composed primarily of the anterior primary divisions of C2 and C3, while the greater occipital is made up largely of the posterior primary branch of C2. That there is a relation between the trigeminal and occipital nerves has long been recognized clinically. Herpes of the first trigeminal division seldom crosses the midline, but not infrequently moves back to include the occipital area. One recent patient had a high cervical rhizotomy for intractable occipital neuralgia. Postoperatively she showed herpes on both the upper and lower lip on the ipsilateral side. It should be noted that, after the trigeminal compression procedure, postoperative herpes in the appropriate divisions seems to occur just as frequently as after rhizotomy.[9] Other examples of occipital trigeminal relationship are seen in neck injuries with facial and retroorbital pain relieved by occipital nerve block. Recently Skillern has discussed this relationship in detail.[10]

Thus, in March 1954, it was decided to try blocks of the occipital nerve as well as the greater auricular nerve in trigeminal neuralgia. The first patient on whom this was attempted illustrates many of the findings substantiated by further trials and will be described in some detail.

A 63 year old white man had trigeminal neuralgia in the left third division. He had had typical recurrent lancinating pain intermittently for 17 years. He had no pain on the right and none in the tongue. On May 27, 1952, a trigeminal decompression of the third division was effected by enlarging the left foramen ovale. Following this procedure there was complete relief of pain for 18 months and then a recurrence of gradually increasing severity. Neurologic examination revealed only a moderate degree of hypalgesia to pinprick and touch in the left third division. The patient's pain was all in the left third division. He was having frequent severe spontaneous pain. His pain could also be triggered by touching either his left lower lip or the hair of his temple about one inch above and in front of the left ear. It was felt that the trigger point was in the third division in about the area where the auriculotemporal nerve, supraorbital nerve, and occipital nerve areas would meet. Xylocaine was injected, blocking his left greater auricular nerve. He shortly had cessation of all spontaneous pain in his left third division and would no longer trigger off his lower lip. However, he still fired readily from the trigger point on his scalp, although mandibular pain was only approximately 50 per cent as severe. After 15 minutes, 5 cc. of 1 per cent xylocaine was injected into the left occipital nerve. Although the area of anesthesia did not reach forward to the described trigger area, he shortly ceased to fire from his scalp and was completely free of pain. When seen the next morning his symptoms had returned unchanged. Repeat blocks were done with identical results. Subsequently the injections were done with saline without benefit. On March 31, 1954 a compression procedure of the posterior trigeminal root was carried out with complete relief of symptoms to the present time.

Although this is a preliminary report and the number of cases of occipital and greater auricular nerve block is still small, there are several findings which we believe to be of interest and significance if they are substantiated by subsequent investigation.

1. Unlike Wyburn-Mason, we are unable to find any clear-cut pattern. There have been several cases of only third division involvement with no tongue pain where greater auricular block has not helped significantly. On the other hand, there is one case of severe pain in both the second and third divisions including the tongue, with trigger points in all three divisions, where greater au-

ricular block gave complete and immediate relief on two separate occasions.

2. However, there definitely seems to be a relationship between the division in which the pain or trigger is located and the nerve blocked. If anesthesia is produced in the contiguous or overlapping area, the results seem to be better. Thus we usually block the greater auricular, and, at times, the lesser occipital and cutaneous colli branches for third division pain and the occipital for first division pain (rare) or trigger (more common). As an example, one woman had severe third division pain and only minimal second division pain. After section of the greater auricular nerve, she has no third division pain but now complains about second division pain.

3. Regardless of contiguous areas, the occipital and greater auricular nerves seem to have a reinforcement or summation value. If a block of one does not completely relieve the pain, blocking the other nerve will sometimes add to the effect regardless of the division in which the pain is centered.

4. At the present time there does not appear to be any relationship between the severity or the length of history of pain and the success of nerve block.

5. It is interesting to note that local block of the greater auricular nerve in trigeminal pain may at times apparently interrupt a pain cycle and give relief for considerable time. In most cases, however, the pain soon returns unchanged. In a number of cases patients have complained bitterly that, after the local anesthetic wore off, the pain seemed definitely increased in severity.

POSSIBLE MECHANISMS

In view of the foregoing, the authors cannot refrain from at least speculating regarding the role of the compression procedure and peripheral nerve blocks in the mechanism of relief of the tic pain. As far as the compression procedure is concerned, we admittedly do not know just what fibers are altered by the pressure. Clinically, two findings after the compression procedure are of interest. There is usually an area of hypalgesia to pinprick and touch, most marked in the third division. This usually subsides in a few days, although a minimal sensory deficit may persist. It is felt that the technic of the procedure explains the fact that the mandibular branch is most involved, even where attempts were made to compress the second division fibers selectively. In stripping up the dura to reach the Gasserian ganglion, considerable trauma must invariably be inflicted on the third division.

The second unusual clinical finding following trigeminal compression is that, while most people are very thankful that they have no real anesthesia (and many have experienced this after previous alcohol blocks), subjective numbness over the trigeminal distribution has been noted, although no objective loss could be demonstrated by testing the usual modalities of sensation. How much of this must be interpreted as psychologic is difficult to determine.

Thus, on hypothetical grounds, the effect of the compression procedure would seem to be most likely due to decreasing the total unit number of impulses that the trigeminal nerve is able to convey, rather than selective destruction of any one type of sensory fiber. As yet we have not been able to study any of the postcompression trigeminal nerves microscopically as there have been no deaths in this group of 28 cases.

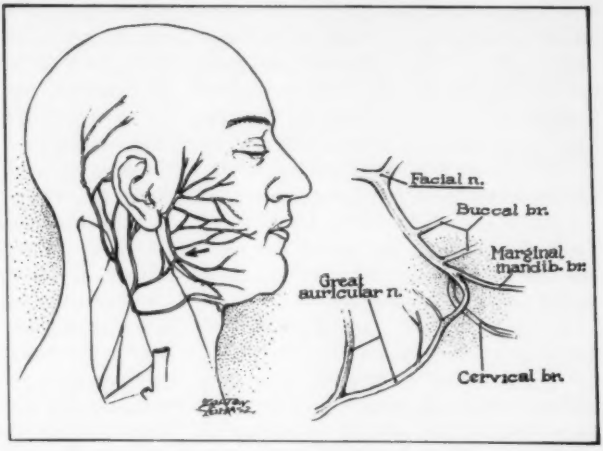

FIG. 2. Connection between the greater auricular and facial nerves. Drawn from a cadaver dissection.

In trying to correlate the findings on greater auricular and occipital nerve block with the other known facts in tic douloureux, one must first think of the possibility of a double peripheral sensory innervation. Weddell[11,12] has shown that a unit area of skin apparently has sensory fibers from at least two directions. The phenomenon of overlap, as shown by Sherrington's spinal root section, is well known. If fibers from the occipital and greater auricular nerves extend into the area of the trigeminal nerve, they may well be analogous. It has long been known that occipital nerve fibers anatomically extend forward beyond the posterior limits of the ophthalmic division of the trigeminal. The greater auricular nerve has a large branch that joins with the facial nerve (figure 2). Many anastomoses between cranial nerves and cervical branches have been described anatomically, but an exact knowledge of many of their physiologic functions has lagged behind.

The nervous system, unlike the vascular, is usually fairly constant in its development. Yet almost all standard texts refer to the unexplained irregularities in the borders of the trigeminal area and mention great individual variations. This may well depend on which nerve is under study and the method of examination used. If one uses response to pinprick where one nerve is blocked in an area where cutaneous innervation is known to be overlapped, the remarkable finding is the constant sharp line of demarcation which the patient will invariably acknowledge subjectively. If one uses a different test method, such as touch, the boundary will be quite different at times, and there may be a gradual gradient zone. In view of the now established concept that each modality of sensation has its own separate and unique end organs and afferent fibers, this leads one to wonder just what type of endings might be included in these overlapping areas.

How complicated these connections can become in a pathologic situation may be illustrated by a recent case of auriculotemporal (Frey) syndrome.[13,14]

The patient had had the facial nerve injured in childhood and now had excessive sweating in the region of the temple when eating or thinking of food. Before sectioning his auriculotemporal nerve, test blocks were carried out, including one of the greater auricular nerve. This produced the expected area of anesthesia but also a slight but definite hypalgesia in the trigeminal area to the midline, most marked in the third and least in the first division.

Another illustration of how little we know of the direction of pain impulses or "referred pain" in this area is seen in the following case. A 43 year old white male physiotherapist, with no history of facial pain, had his teeth cleaned routinely. Following this his gums were sore and on biting or brushing his left teeth he experienced sudden discreet stabbing "tics" of pain in his left ear lobe only, definitely in the area of the greater auricular nerve.

Another illustrative case is that of a recent patient with whipsnap neck injury, who had a unilateral area of anesthesia over the greater occipital nerve distribution. He complained that shaving the neck under his chin on the affected side produced a severe pain referred to the anesthetic occipital area.

In view of the many cases of continuing clinically complete anesthesia in the trigeminal areas after posterior rhizotomy of the fifth cranial nerve, any attempt to hypothecate a cervical innervation as well to the majority of the trigeminal area would be difficult indeed to substantiate, although this may prove to be the answer, as Wyburn-Mason apparently believed.

In trying to correlate the results from trigeminal compression and greater auricular occipital nerve blocks in trigeminal neuralgia, one cannot draw final conclusions. But, after the syndrome of tic douloureux is established, if blocking the higher cervical nerves can stop the pain even in a few instances, there must be a connection in the pain mechanism. It seems to us this connection is most likely a central one, most probably in the upper cervical cord where the descending sensory nucleus of the fifth cranial nerve must be in a juxtaposition with the incoming upper cervical sensory fibers. Just how these two areas are related is not known. Even after much investigation[4] the exact peripheral distribution in the descending nucleus of the fifth cranial nerve is not clear. To quote Nielsen's recent text,[15] "It's (the trigeminal) sensory descending root (for perception of pain and temperature only) extends downward through the entire length of the medulla joining its nucleus which lies mesial to it . . . It has long been taught that in lesions of the descending root of the fifth nerve the loss is of the so-called onion peel distribution, such that the highest phylogenetic portion is supplied by the highest portion of the root and nucleus. Differential diagnoses of disease of the brainstem have been based on this supposed anatomic fact. Studies based on thrombosis of the posterior inferior cerebellar artery, syringobulbia, and, above all, on the results of tractotomy for relief of trigeminal pain seem rather to refute such a theory. Tractotomy causes loss of pain and temperature sense according to the distribution of the three peripheral divisions. This harmonizes with Bing's diagram rather than with the classical teaching."

It has always seemed to the authors that, regardless of the original cause, once the syndrome of tic douloureux was

established, there could be little doubt of the central nature of the typical explosive pain. The pain, so unlike any neuralgia or neuritis elsewhere, must be a sudden release of an abnormally large number of pain impulses, which presumably pass through the thalamus to reach the cortex and consciousness. At times it may be perpetuated for a considerable length of time. At just what level this hypothetical, unique, sensory "epileptogenic" focus is located is, of course, unknown, but it cannot conceivably be peripheral. The concept of a central sensory seizure is unique, but so is the pain in trigeminal or glossopharyngeal neuralgia, and so is the anatomic and physiologic area involved. The term "sensory epilepsy" has been used for years but refers to a typical motor cortical seizure which is triggered by known incoming sensory stimuli and is hardly analogous to the present hypothesis. The fact that motor discharges from the nearby seventh nerve nucleus in the form of true facial tic movements may at times accompany the pains of tic douloureux lends some substantiation to this electrical concept. The fact that the pain may remain limited to a single division for a long period fits in well with our belief that this focus is probably at a low level in the brainstem in relation to the nucleus of the fifth nerve.

Suppose for the sake of discussion we tentatively accept this hypothetical central focus of pain in trigeminal neuralgia. One must then consider what is necessary to make it "fire" or discharge. Here we find the trigger mechanism playing its role. Trigger zones are not limited to tic douloureux but are found in other types of peripheral "referred pain" mechanisms and have been extensively studied by Travell.[16] However, these deep trigger zones in myofascial syndromes are dissimilar to the light touch or movement needed to trigger tic douloureux. Only in certain sympathetic involvements, such as causalgia, is anything as sensitive found. Feeding into the substantia gelatinosa of Rolando are incoming sensory impulses from not only the trigeminal but the upper cervical sensory nerves on the same side. They probably are not all of equal importance, either as to the volume of incoming impulses or the location of their endings in relation to this hypothetical abnormal "internuncial pool" awaiting discharge. We do not recall ever seeing tic pain simultaneously in the first and third divisions, for example, with no involvement of the second.

There is a time factor. Once a pain is triggered there is often a refractory period during which the trigger zone can be touched safely. Thus, once a tic has started we often see the patient pressing on his face with masochistic determination. It should be noted that the trigger zones are usually located in peripheral areas with a maximum number of sensory endings in a unit area, such as around the eyebrow, the hair of the temple, or the lip. One would expect, as is found clinically, that the focus (pain location) would be more constant than the location of the firing mechanism (trigger zone). The trigger zones are much more unstable and reportedly can even be altered psychologically, as under hypnosis.

As the course of the disease progresses, it must be due to one of two factors or a combination of both: 1) Either due to repeated use of the focus or to progression of the underlying etiologic cause (such as arteriosclerosis), the total number of incoming units needed per

given time to fire the pain focus steadily declines. 2) Or due to progressive peripheral involvement of the incoming nerves, such as infection around the teeth or angle tumor irritating the branches of the trigeminal, the total unit intake per time increases to a critical level. Finally the point is reached where only a small increase in input in just the right area, such as touching the lip or moving the face, will be sufficient to fire, the location of the trigger zone peripherally being a function of the number of peripheral endings and also the location of the central endings of these fibers in relation to the central focus. Eventually a point is reached where the normal input such as from proprioception without any objective external sensory stimulation is above the critical level and we find spontaneous tic pain.

One must now see if other known observations in trigeminal neuralgia fit in with this hypothetical scheme.

1. Why are there so many third division pains and so few first division pains? This may well be a function of the location of the placement of the central endings, still unknown. Or it may be that an individual with a predisposition toward tic may establish his focus in the area of maximum incoming stimuli, and the third division with the teeth and movable mandible is certainly more often liable to be pathologically irritated (and stimulated?) than the ophthalmic division.

Before dismissing the phrase "predisposition to tic" so lightly, one case in this series is of interest. A 45 year old white man had typical tic since age 17. His mother had tic pains from an early age on the same side. While this hereditary factor may have been due to a peripheral anomaly, it certainly seems more likely to indicate a central type of defect.

2. Why is tic unilateral in all but 2 to 4 per cent? This should be expected because, even if centrally there was an equal predisposition bilaterally to the establishment of a firing focus, the external trauma to which the peripheral division of the trigeminal is subjected is usually not symmetric. Consequently, the incoming volume might be expected to be greater on one side. There certainly can be no doubt as to the peripheral element in the etiology of this disease. Contrary to Dandy, it may well be peripheral to the Gasserian ganglion. Several of the patients in this series had their tic pains start on the same side soon after dental surgery, one at a very early age where there was no sign of trigeminal pain as a reason for the dental work. Also contrary to Dandy's belief, there may be either a traumatic or hereditary factor in the etiology. There were two cases where there was a definite history of severe trauma to the head on the same side. It is unusual that there are so many bilateral tics. In this series three patients had had bilateral pain so severe as to necessitate some type of pain relief procedure on both sides. Several others had had some minor tics on the "good" side.

In this regard two patients who had trigeminal rhizotomies prior to this series are of interest. These two patients had typical third division tic but also had trigger zones outside the trigeminal area. One man fired from pressure on his big toe. The second case was an 83 year old female who had right third tic pain readily triggered off her lower lip. She also held her right hand carefully protected the same as a patient with causalgia. Any movement of her thumb, such as shaking hands, immediately triggered

her right third division pain. These two cases were considered to be evidence of the central stimulation of the pain mechanism. However, on later reflection it was difficult to explain the fact that the trigger area was on the same side as the pain, as the majority of the sensory impulses should have crossed in the cord. It is obvious that these may have represented some type of palmo-mental reflex where a slight, perhaps imperceptible, movement of the platysma or skin set off the more usual type of trigger area in the affected third division.

3. How do we explain these organic lesions, such as tumors of the cerebellopontine angle, which seem to cause tic? In the first place, many of these people have a different type of trigeminal pain, not at all similar to tic douloureux. This is in line with attempts to produce pain by artificial stimulation. The pain from electrical stimulation of the posterior root or entrance of a needle into a peripheral branch is not at all similar to the tic pain. In approximately 3 per cent of angle tumors with true tic pain, the irritative lesions may well have acted only to increase the total inflow in a patient with a potential central tic focus. One must remember the tremendous number of patients with angle neoplasms and the even larger number with poor dental work who never have anything at all resembling tic douloureux. Dandy has repeatedly pointed out that lesions behind the Gasserian ganglion and involving the sensory root are particularly liable to produce true tic pains. Whether pathologic lesions involving the peripheral portions of the trigeminal or the sensory root itself can be assumed to have increased the total inflow of afferent impulses by irritation must at present be merely a matter of conjecture. It may well be that it is an unusual pattern or balance of inflow with an actual decrease in the total, as may be the case in other types of organic pain syndromes such as tabetic crisis or postherpetic neuralgia where there is clinical evidence of actual nerve damage.

4. There remain other considerations of trigeminal pain which cannot be fitted well into this or any other hypothesis. One of these is the effect of the seasons. Tic has long been known to recur in the spring and fall.

5. Lastly, we must fit the various surgical treatments into this hypothetical scheme. Anything that decreases the inflow of sensory impulses into this critical area in the brainstem should be beneficial. Attacking the trigeminal itself on theoretical grounds alone should be most effective. And keeping in mind not only the total units of inflow but their central endings around this hypothetical focus, one would expect better success when the painful division itself was attacked. That the affected division itself need not always be attacked is often shown by the subsidence of pain in more than one division of the trigeminal after only a single alcohol block of the most painful division. One would, of course, expect best results from section of the trigeminal. However, compression seems to be adequate. Recurrence may develop if the fibers are not permanently destroyed by compression. Of the 28 trigeminal compressions reported here, none has recurred as yet but the time is too short for adequate interpretation. However, it was destruction of the trigeminal with its sequelae of anesthesia that the compression procedure was designed to obviate. With modern anesthesiology and surgical technics, reoperation seems to be less of a

threat than trigeminal anesthesia or the risk of medullary tractotomy.

That even trigeminal section may not be adequate is seen in the rare case presented by Wyburn-Mason, where trigeminal "ghost pains" persisted until the greater auricular nerve was also cut. Here one must recall at once the work of Foerster who recorded pain from stimulation of the distal ends of sectioned cutaneous nerves in the human subject. This pain was abolished by section of adjacent overlapping cutaneous nerves. Thus these so-called "ghost pains" may be explained on either a peripheral or a central basis.

Blocking the high cervical nerves without attacking the fifth nerve itself, may stop the trigeminal pain in some cases. While the number of such cases where this may be possible or permanently sufficient will be small, it certainly deserves further investigation.

How the medical treatments, which are undeniably effective in some cases, fit into this scheme is also unknown. Some may reduce the sensory inflow by improving the irritating peripheral abnormality. Others may raise the critical level needed to fire the central focus. However, while B_{12}, trilene, and possibly stilbamidine, may work at times, there is still no safe and surely effective medical treatment. It is hoped that one may be forthcoming.

SUMMARY

Past attempts to find a more effective surgical treatment for tic douloureux have been mentioned briefly. The similar results of Taarnhoj in decompressing the posterior root of the trigeminal nerve and of our ten cases of a more anterior peripheral decompression were cited. Both gave similar immediate relief but with a significant recurrence rate. In an attempt to find the common factor in both of these so-called "decompression" procedures, a trigeminal compression procedure was devised.[17] This has been done in 28 cases with uniform relief of symptoms and no surgical morbidity. At the present time there has been no case of recurrence up to 15 months. To further study the pain mechanism in trigeminal neuralgia, greater auricular and greater occipital nerve blocks have been carried out. In this presentation a tentative hypothesis of a possible central pain mechanism has been outlined.

CONCLUSIONS

1. Compression may be the important factor in the recent trigeminal "decompression" procedures. Trigeminal compression in our practice is the standard surgical procedure for trigeminal neuralgia. It will probably continue to be so, unless a medical treatment is found or a high recurrence rate, as yet not indicated, forces abandonment. It is of especial value in bilateral disease.

2. Further investigation of cervical nerve block is indicated. Further data are needed in working out the mechanisms of this disease. Perhaps no patient should be subjected to craniotomy until the simple procedure of local cervical nerve block has been tried.

3. At the present time the preponderance of evidence seems to indicate some central type of mechanism in trigeminal pain, regardless of the underlying etiology.

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■ There is a very curious symptom which seems to belong exclusively to diseases of the spinal cord (at least we do not know of any case of disease of the encephalon in which this symptom has existed, the spinal cord being healthy). It consists in a spasm of the flexor muscles of the lower limbs, spasm which is so powerful that the anterior parts of the thighs come almost in contact with the abdomen, while the heels are drawn up so as to touch the back parts of the thighs.

Were it true, as admitted by Bellingeri and Valentin, that the anterior columns of the spinal cord are a bundle of nerve-fibres animating the flexor muscles, and that the posterior columns contain the nerve-fibers animating the extensor muscles; and were it true, also, as admitted by almost all physiologists, that the nerve-fibres have the same excitability in the spinal cord as in the trunks and branches of nerves, we should see flexion produced in cases of tumors or diseases exciting the anterior columns, and extension in cases of excitation of the posterior columns. Now, in examining pathological cases in this respect, we find that there are a great many more in which neither of these symptoms have existed than cases in which they have been observed with the peculiar alteration which should be connected with them.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CLINICAL PATHOLOGIC CONFERENCE

E. P. Richardson, Jr., M.D. Section Editor

Presented by *Russell N. DeJong, M.D. and Jose Bebin, M.D., Ph.D.*

CASE PRESENTATION

A white girl, born on December 28, 1950, was first examined at the age of 27 months, when she was referred for evaluation because of progressive difficulty in walking.

The child had been born about two weeks prematurely after an uneventful pregnancy. Birth was precipitate, without anesthesia; the mother was in labor only six minutes. The patient weighed 6 pounds, 6 ounces at birth, and as far as the mother knows there was no cyanosis, icterus, difficulty in breathing, or delay in sucking. The child apparently developed normally; she grasped objects at seven months, sat up at eight months, drank from a cup at ten months, talked using simple words at 12 months, and talked in sentences at 18 months. She weighed 19 pounds at the age of one year. The parents did state, however, that the patient's development was definitely slower than that of her older sibling. She had never crawled, but began walking without support at 13 months. It was noted from the very beginning, however, that her knees appeared to be "weak," her right foot "pointed out," and she fell frequently. She had difficulty walking on uneven ground, and had never been seen to run. She had always been nervous and emotionally "high strung;" she was somewhat irritable, became frightened easily, tired readily, was "sensitive," and sometimes trembled and became rigid when excited. The parents believed the child to be alert mentally, they felt that she talked normally for her age, and stated that she could eat by herself and could see and hear without difficulty. She dressed herself to a certain extent, although she was not toilet trained.

At the age of 18 months the patient had chickenpox, and two months later there was an episode of severe diarrhea for two weeks. It was noticed at this time that her eyes were crossed. When she was about 20 months of age she was taken to an ophthalmologist who stated that there was a slight squint of the left eye and that she was farsighted. A patch was placed over the right eye, which seemed to improve the squint, and thereafter it was noted only occasionally. She was given glasses at 26 months but did not use them often.

When the child was 23 months of age the parents noticed that there was more definite difficulty with her legs; her gait became weaker and she walked less without support. The left foot as well as the right became rotated externally, and she developed abnormal flexion at the knees and walked in a somewhat crouched position. She was taken to an orthopedic surgeon who, after roentgenograms of the hips and pelvis, stated that there was nothing wrong with the legs themselves and hinted that the patient might have either dystrophy or cerebral palsy. When the patient was 26 months of age she had severe "intestinal flu" with vomiting, chills, and fever. She spent a short period of time in bed, and thereafter did not walk alone. She began to crawl, which she had not done before. She could pull herself to a standing position and stand alone, but she did not walk without support. She was still able to climb stairs. Thereafter the difficulty in walking was progressive. There had been no convulsions, although questioning revealed that there had been three episodes during which the child might possibly have had seizures. On one

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occasion during her first month she was seen to become rigid and "tremble all over" momentarily while the mother was holding her. At the age of three months there was a similar episode, and during this the eyes rolled back for a few seconds. During the febrile illness at 26 months she had an episode in which she "shook all over," but the mother was told that this was due to a chill.

The father and mother were living and well, and an older sibling, aged 5, was normal in every respect. There was no family history of similar difficulties. One maternal uncle was said to have had "St. Vitus Dance" as a child.

The first examination on March 31, 1953 was carried out with difficulty because the child was frightened and cried frequently. She would not stand alone and would walk only when holding her father's hand. The weight was 29 pounds and she seemed to be normally developed for her age. She understood commands, answered occasionally, but actually talked very little and the speech was quite infantile. On command she would transfer a pencil from one hand into the other and then hand it to the examiner. The general physical examination, aside from a heart rate of 200, was within normal limits. The fontanelles were closed. The patient walked with a shuffling gait which had a definite spastic element. The pupils were moderately dilated, but were equal and reacted to light. There was an alternating strabismus. The eyes were rather prominent and the left palpebral fissure was wider than the right. The upper extremities were tremulous on occasion, but were used quite well and coordination seemed to be satisfactory; there seemed to be a slight increase in tone bilaterally and the reflexes were moderately hyperactive. The lower extremities, especially the right, were definitely spastic, with hyperactive patellar and achilles reflexes and bilateral Babinski signs. Abdominal reflexes were absent. The sensory examination was grossly normal.

The child was admitted to the University Hospital on April 20, 1953, and discharged on May 2, 1953. Examination at this time was similar to that noted a month previously. Laboratory studies of the blood and urine were within normal limits except for a leukocytosis of 18,450 at the time of admission, which did not persist; later blood counts were entirely normal. The differential counts were normal. Examination of the lumbar spinal fluid showed a negative Kahn serologic reaction, a total protein of 150 mg. per 100 cc., and a colloidal gold curve of 0011000000. The globulin reaction was 3 plus. The ventricular fluid showed a total protein of 68 mg. per 100 cc., a colloidal gold curve of 0000000000, and a globulin of 2 plus. Roentgenograms of the skull, spine, and chest were all normal. An electroencephalogram showed a background of 5.5 to 6 per second waves in the usual voltage distribution. During sleep there was anterior displacement of voltage parasagitally; the patient did not go through a spindle stage, although occasional spindles were noted toward the end of sleep. There was no homologous asymmetry and no focus. The interpretation was: "The record is mildly slow, abnormal, and stereotyped, and is consistent with some mild degenerative condition of the brain, although certainly not diagnostic."

The patient was seen by a consultant from the department of orthopedic surgery, who felt that this was not a typical cerebral palsy and suspected some type of degenerative brain disease. A consultant from the department of ophthalmology found an accommodative intermittent convergent strabismus. A consultant from the department of physical medicine favored a diagnosis of cerebral palsy and doubted that there had been much progression of her difficulty. This was also the impression of the pediatric consultant. Psychologic testing, using the Cattell Infant Scale, gave the patient an intelligence quotient of 101. The child, however, performed the tests slowly, perseveration was marked, and motor performance was definitely hampered by a tremor and poor muscle control.

A ventriculogram was done on April 28, 1953 under Avertin anesthesia. The brain tended to extrude but later pulsated, and this was thought to be the effect of anesthesia. The ventriculogram was reported as normal, although the fourth ventricle did not fill. The postoperative course was normal.

The patient was next seen on July 24, 1953. The parents reported further progression of symptoms. She no longer tried to walk or raise herself to a sitting or standing position and no longer crawled. When recumbent she could only prop herself up on her elbows. When sitting she would lose her balance and fall to one side. The parents had noted periods when she would seem to be staring into space, although she would respond when spoken to. She had marked difficulty in getting her food to her mouth and she preferred to be fed. She seemed to be tired constantly, did not talk as much as she had, and cried a great deal. The parents had noticed increased trembling of her extremities. They stated, however, that she was less spastic and she had been trying to learn to ride a tricycle with assistance.

On examination the patient was unable to sit without support. The eyes seemed quite prominent, and the inequality of the palpebral

fissures was again noted. There was some strabismus, but definite ocular palsies could not be diagnosed. The fundi were normal, with no change of either the disks or the macular areas. The extremities seemed to be somewhat less hypertonic. Babinski responses were found bilaterally. Tremor and incoordination were more marked. It was thought that the disability was progressing and, because the parents questioned a possible infectious or inflammatory etiology, the patient was placed on Terramycin.

The patient was last seen on September 14, 1953. In August she again had "intestinal flu." Until that time she could raise herself up on her elbows, look around, smile, and see. In September she stopped talking and began having difficulty swallowing, so that she was placed on a liquid diet and bottle fed. At this time her eyes were noted to quiver constantly. She complained of pain when on her back and when her back was flexed, and consequently lay only on her stomach; she no longer raised herself on her elbows. It was reported that she was receiving phenobarbital and Tolserol. Examination at this time showed a progressive disability and weakness.

In November 1953 the patient had a fever which was as high as 106° F. for three days. On the third day she had a slight convulsion. She was taken to a local hospital and no cause for the fever was found. It was stated that no cells were found in the spinal fluid. About this time the patient lost her eyesight, but her hearing was said to be unimpaired. In December she again had a high fever for four days, but it was not as severe as the previous one, and she was treated with aspirin and alcohol baths. Fever recurred in February 1954 and this was followed by vomiting for two weeks. The parents reported that she was tense and stiff most of the time, and they were unable to rotate her head because of the stiffness of her neck. She had developed more difficulty swallowing and regurgitated part of her formula. In April it was noted that the patient's weight was down to 12 to 15 pounds. The patient was given symptomatic treatment with small amounts of sedatives and analgesics, but there was progressive deterioration until her death on December 9, 1954, shortly before her fourth birthday.

CLINICAL DISCUSSION

DR. RUSSELL N. DE JONG: We have been given a rather graphic description of progressive physical and mental deterioration in this little girl, who was at one time said to have been normal or nearly so. This patient was only seen at the University Hospital and by me on a few occasions, but we have the benefit of typed notes by the parents and periodic interviews with them which give the details of the course during the last 15 months of her life. Her parents were good observers and apparently very objective in their observations, but it is often difficult for parents to be entirely objective, and we have had experiences in the past where very intelligent parents have for long periods of time denied the progressing disability and deterioration in their children, even though such was very obvious to outsiders. This denial is probably in part "wishful thinking," and is unconscious rather than conscious. It is of interest that both the pediatric and the physical medicine consultants doubted the reliability of the parents' observations and felt that this was not a progressive change but that the child had always had more disability than the parents admitted; they did concede, however, that the febrile episodes might have aggravated the difficulty. The pediatric consultant, for instance, in referring to these epsidoes, stated, "These often set back normal children to a certain degree and handicapped children even more, and we can hope, therefore, that this does not represent a true failure of progress or a deterioration." The later course of this child's illness, however, confirms the reliability of the parents' observations from the beginning.

To review the essential factors in the history briefly, the first symptoms were those of motor disability with a gradual change in the patient's motor functions, especially her ability to walk. We do find that her gait had been slightly abnormal from the beginning in that her knees were weak, her right leg was externally rotated, and she fell frequently. But, as we review the entire course, we learn that there was a progressive deterioration from a once established level, even though that may have been below normal. This involved first the lower extremities, and later the upper extremities, the spinal muscles, the neck, and, finally,

swallowing and speech. As far as the mental status is concerned, the child had always been a little slower than her sibling, but when we first saw her our tests showed her intellectual level to be normal for her age, even though the tests were performed with difficulty because of her motor disability. Later there also was progressive intellectual deterioration, but this did not progress as rapidly as the motor change. Convulsions apparently were not prominent, although the slight episodes dating from the first month, which the parents described so accurately, were probably seizures, and later there were spasms and absences. In addition, we have a history of tremors and ataxia and later of blindness. Neurologic examinations confirmed the data from the history. The most pertinent laboratory finding was an elevated spinal fluid protein. Thus we have the story of a long, tedious deteriorative process, although this child was kept alive until she was nearly four years of age.

Cases of this sort are seen fairly frequently, but they are always diagnostic and prognostic problems as far as I am concerned. I think that we can fairly readily eliminate as diagnostic possibilities such categories as neoplasm, inflammatory or infectious process, specific vascular disease, sequela of trauma, toxic involvement, and congenital abnormality of development. I realize that I should not dismiss too lightly the possibility of infiltrating neoplasm, although I believe that the very progressive course, long duration, and absence of increase in intracranial pressure, as well as the normal ventriculogram, are against this possibility. We do have a history of chickenpox shortly before the parents first noted symptoms, and of later recurrent febrile episodes, but I feel that the process was already present prior to the former and the latter were secondary to the disease process rather than etiologic. Under infections we should also consider toxoplasmosis, but ocular and roentgen evidences of this were not apparent. With the above possibilities eliminated, we are more or less forced to classify the disease in that motley collection termed as "degenerative processes." These are those diseases whose etiology and mode of production are, in most cases, not known. Some are hereditary and others are not. We presuppose in many of them an inherent disorder of metabolism, a low grade unknown infectious process, and unknown "toxic" etiology, or what Gowers has termed abiotrophy. By this is meant a nervous system endowed with inadequate vital resistance or capacity to survive. Certain structures or cells do not have the normal capacity to exist for their usual span, and cease to function or degenerate. We refer to some diseases of older life as "degenerative" because of inadequate knowledge regarding their pathophysiology. Among these may be classified such conditions as multiple sclerosis, Huntington's chorea, Parkinson's disease, and so forth. However, there are many degenerative processes of infancy and childhood which make up an important but puzzling chapter of pediatric neurology. The child is usually normal or nearly normal at birth, in contrast to one with congenital defects and disturbances of development. The symptoms are usually progressive, but often the onset is so insidious that even the most careful observer cannot set a definite date to the beginning of the change; the deterioration is so slowly progressive that it is difficult to be certain, unless one follows the course of the disease, that such change is taking place.

In order to attempt to arrive at a diagnosis in a case of this sort we should know, if at all possible, two things: 1) the time of onset; 2) the site of predominant pathologic change. In determining the time of onset, we should know whether this difficulty was prenatal and date from before birth, whether it is related to factors at the time of birth, or whether it is postnatal in onset. Here we have a history of premature birth, but no evidence of any abnormality on the part of the mother during pregnancy. Birth was precipitate, but the immediate postnatal condition was said to be entirely normal,

and early development was also normal, although we find that from the beginning some of the motor functions, and possibly some of the intellectual functions as well, contrasted unfavorably with those of the older sibling. Therefore, we must assume that this child was born with a poorly endowed nervous system but without apparent abnormalities. Consequently she cannot be classified in the group of cerebral palsies dating from birth. As she grew physically and as time passed there was certainly evidence of abiotrophy, or progressive impairment of function of certain portions of the nervous system.

As far as site of involvement is concerned, there is evidence that there was rather widespread involvement; there was motor change resulting in spasticity, there were tremors with ataxia, there were some convulsive manifestations, there was intellectual deterioration, and finally blindness. Therefore, we have to consider that there probably was involvement of the cortex in more than one area, the association pathways, the deeper gray structures, the cerebellum or its connections, and possibly pontine and medullary centers.

Ford has given us one of the best classifications of the heredofamilial and degenerative diseases of the nervous system in children, and he classifies them as follows: diffuse and focal degenerations affecting chiefly the white matter; degenerations involving the cerebral gray matter; specific cellular degenerations with lipoid or amyloid deposits; and degenerations affecting certain parts of the nervous system such as the basal ganglia, the cerebellum, the fiber tracts of the spinal cord, the peripheral nerves, or the retina and optic nerves.[1] I think that the picture here must fit into one or more of the first three categories.

I believe that most clinicians would think first, in a case of this kind, of white matter degeneration of the Schilder or related varieties. In these the symptoms and clinical course vary, but the clinical picture here is compatible with such a diagnosis. The outstanding symptoms in most cases of Schilder's disease are progressive motor difficulty, either a hemiplegia or paraplegia leading to decerebrate rigidity, visual field defects leading to blindness, deafness, aphasia, convulsions, and a final complete dementia. The course here is a little long for Schilder's disease, but not necessarily so, and a high spinal fluid protein is sometimes seen in this condition. The fact that motor involvement was so slowly progressive and preceded intellectual change and also that convulsions played a minor part might be against the diagnosis of Schilder's disease in this case. The other white matter degenerations, such as those described by Balo, Pelizaeus-Merzbacher, Scholz, Krabbe, and others, cannot in general be differentiated from Schilder's disease, except possibly on the basis of the family history in the Pelizaeus-Merzbacher variety. In all of these the diagnosis is a pathologic and not a clinical one. The type of degeneration described by Greenfield, affecting mainly oligodendroglia and those fiber tracts which are myelinate relatively late, might apply in this case, although this, too, is a pathologic and not a clinical diagnosis.[2,3]

Very few cases of primary degeneration of the gray matter have been described. The most complete study is that of Alpers.[4] In this condition, however, the cardinal symptoms are convulsions, muscular rigidity, athetoid movements, and mental deterioration, with death in status epilepticus; most have a somewhat earlier onset. However, the course in this case might fit into this category also.

As far as the cellular degenerations are concerned, we think mainly of the cerebroretinal degenerations with lipoid infiltrations of the cells, or of the myoclonus epilepsies with either lipoid or amyloid-like bodies in the ganglion cells. The pronounced motor changes, the absence of myoclonus or retinal changes, and the few actual convulsive manifestations more or less eliminate these as a possibility.

Clinically, our picture here, with progres-

sive motor change followed by mental deterioration, blindness, tremors, and ataxia, could be the result of either white or gray matter involvement. From a statistical point of view, one would think first of the white matter degenerations, but the case is not quite typical. The manifestations could also result from cellular loss and necrotic and glial changes in the cerebral cortex, although the hyperkinesias and convulsions usually encountered in gray matter deteriorations were not a part here. Although I realize that cases in which there are degenerative changes in both the white and gray matter are extremely unusual, I would like to suggest, in this case, the possibility of involvement of both, ocurring either simultaneously or consecutively. The changes in the white matter would probably be those of diffuse demyelinization, but possibly without the extensive softening that is encountered in Schilder's and Balo's diseases. There may be more definite involvement of the late myelinating fibers, as in the syndrome described by Greenfield. The alterations in the gray matter might consist of loss of cells, gliosis, and even necrosis; these might be presumed to involve not only the cerebral cortex but also the cerebellum, either the cortex or the dentate nucleus, but it seems to me that the gray matter of the basal ganglia is relatively spared. I would be unable to say whether changes in the cortex occurred first, with secondary demyelinization, or whether those in the white matter were first, with later changes in the cortex, or whether the degeneration of the two areas took place simultaneously.

PATHOLOGIC DISCUSSION

DR. JOSE BEBIN: The brain weighed 939 grams at the autopsy table (normal weight for a child of this age is 1,141 grams). The hemispheres were symmetric and the cerebral convolutions were somewhat reduced in size, with widening of the sulci. Cross section of the brain showed moderate dilatation of the lateral ventricles. No other gross abnormalities were noted in the basal ganglia, thalamus, brainstem, or cerebellum. (Only parts of the brain were received in this laboratory.)

Histologic Description

Sections of the cerebral cortex, basal ganglia, brainstem, and cerebellum were studied with the hematoxylin and eosin, Weil (for myelin), and silver carbonate (Hortega) technics. Red oil was used for staining fat.

Meninges: The leptomeninges appeared moderately thickened and showed some hyaline changes. There was also congestion of the blood vessels and occasionally very moderate perivascular infiltration.

Cerebral cortex: There was diffuse cortical atrophy with marked loss of the ganglion cells. The remaining neurons showed severe chronic degenerative changes; they were shrunken and pyknotic, with corkscrew dendrites. Throughout the cortex there was extensive gliosis, predominantly astrocytic. The silver preparations revealed marked increase of astrocytes in the marginal layer and throughout the cortex. The astrocytes became larger in the deeper layers of the cortex; most of them were of the fibrocytic type (figures 1 and 2).

White matter of the cerebral hemispheres: There was a diffuse demyelinization of the white matter of the convolutions and the centrum ovale. Immediately underneath the cortex there was a marked status spongiosus, forming large round spaces, and there was diffuse demyelinization (figure 3). Through this zone there were very abundant large compound granular corpuscles mingling with large gemistocytic astrocytes, and there was swelling of the oligodendroglia. There was also destruction of myelin sheaths and breakdown of axis cylinders. The silver preparations showed intense gliosis made up of large astrocytes with abundant large thick processes (figures 1 and 2). Preparations counterstained with red oil showed abundant gitter cells and macrophages laden with fat; these were located mainly around blood vessels in the perivascular spaces. In the cortex as well as in the white substance

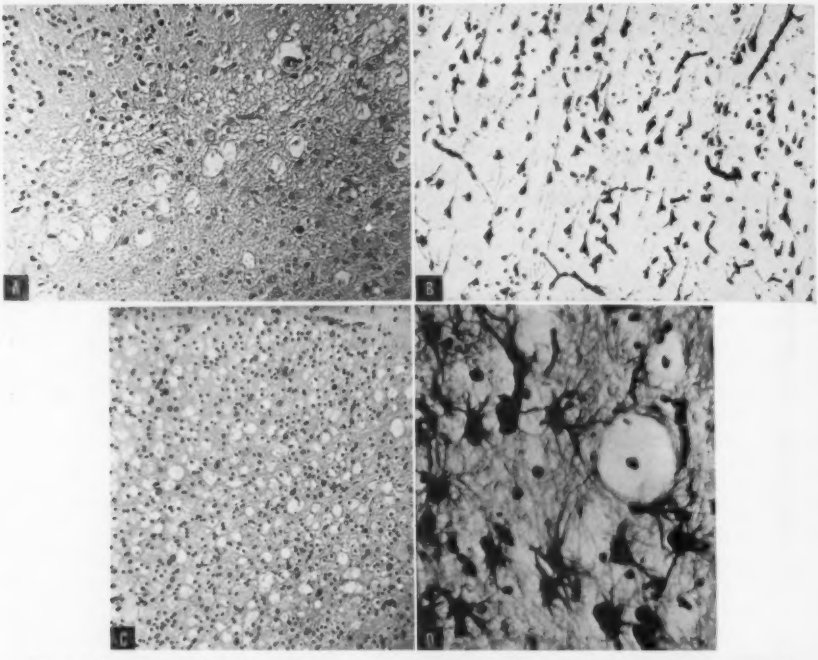

FIG. 1. *A.* Section of the cortex and white matter of the brain (hematoxylin and eosin stain). There is marked spongy state, with proliferation of astrocytes beneath the cortex and swelling of oligodendroglia. *B.* Section of cerebral cortex (silver carbonate stain of Hortega), showing marked chronic degenerative changes in the central neurons. *C.* Section of white matter of cerebrum (hematoxylin and eosin stain), showing spongy state in white matter just beneath the cortex. *D.* Section of white matter of cerebrum (silver carbonate stain of Hortega), showing marked spongy state and proliferation of large astrocytes, the processes of which surround the cavities present in this area.

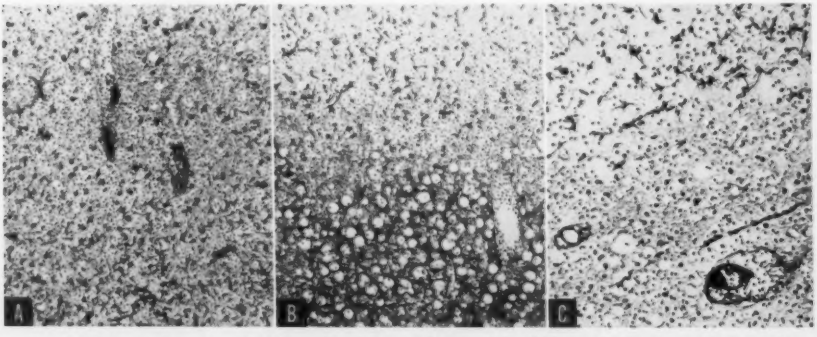

FIG. 2. Sections of cortex and white matter (silver carbonate stain of Hortega), showing marked atrophy and gliosis of the cortex and spongy state in the white matter beneath the cortex.

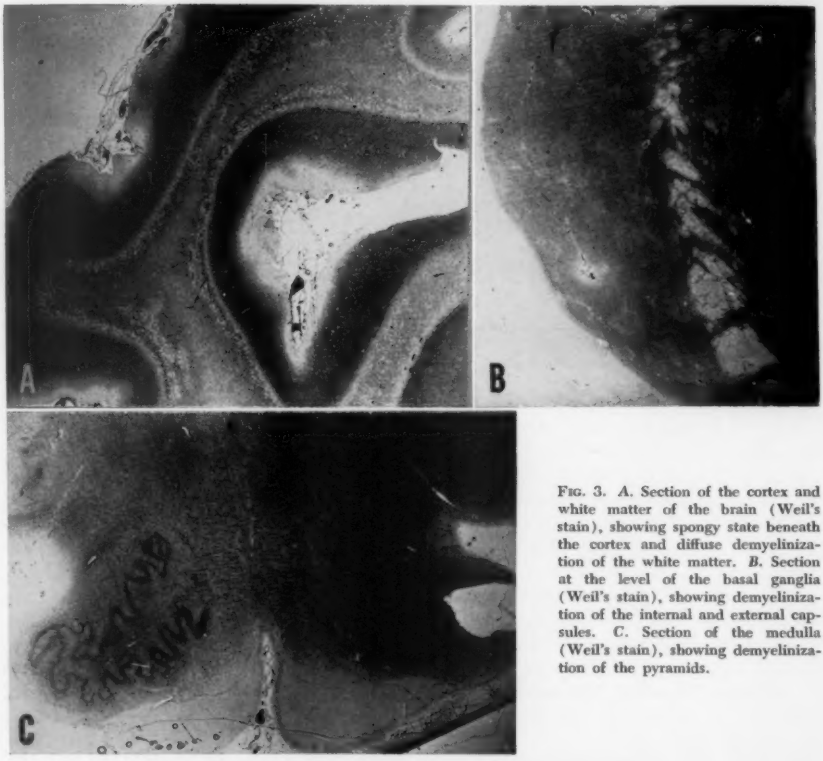

FIG. 3. *A.* Section of the cortex and white matter of the brain (Weil's stain), showing spongy state beneath the cortex and diffuse demyelinization of the white matter. *B.* Section at the level of the basal ganglia (Weil's stain), showing demyelinization of the internal and external capsules. *C.* Section of the medulla (Weil's stain), showing demyelinization of the pyramids.

of the hemispheres there was no evidence of any active inflammatory process and only an occasional small perivascular infiltration by plasma cells and lymphocytes was observed.

Basal ganglia and internal capsule: There was almost complete demyelinization of the internal capsule (figure 3), with marked spongy state, numerous macrophages, and gitter cells and astrocytes. The caudate nucleus and the putamen showed moderate degenerative changes in their neurons, with increase in glial nuclei. The external and extreme capsules also showed intense demyelinization.

Ependyma: The ependyma of the lateral ventricles appeared normal. There was marked increase in astrocytes in the subependymal layer. There was no evidence of inflammation.

Brainstem: In the midbrain there was complete demyelinization of the basis pedunculi. There was a spongy state in the basis pontis and degeneration of the corticospinal fibers. On the left there was a small area of softening with abundant debris and gitter cells perivascularly. The medulla showed diffuse demyelinization, more intense in the pyramids (figure 3). The cranial nerve nuclei (hypoglossal and ambiguous) showed marked degenerative changes of their neurons; many appeared swollen.

Cerebellum: There was marked atrophy of the cerebellar cortex, with loss of the

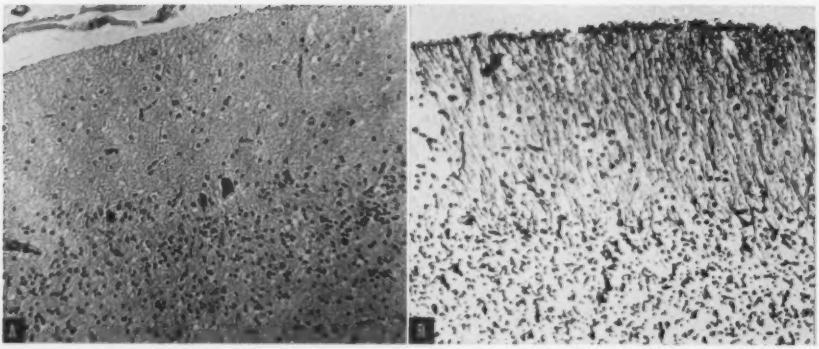

FIG. 4. Sections of the cerebellar cortex: *A*. Hematoxylin and eosin stain. B. Silver carbonate stain of Hortega. There is marked cerebellar atrophy, with loss of Purkinje and granular cells. Intense proliferation of Bergmann's fibers in the molecular layer is evident.

granular and molecular layers and almost complete loss or degeneration of the Purkinje cells (figure 4). Some of the latter remained, but they appeared shrunken and pyknotic. There was extensive astrogliosis throughout. The myelin preparations showed pallor of the white matter, and there was a spongy state with gliosis in the same regions. Silver preparations of the cerebellum showed the most affected parts to be the hemispheres (figure 4). There was marked gliosis of the cerebellar cortex with proliferation of Bergmann's fibers and with astrocytes throughout. There was an absence of parallel fibers and baskets. The dentate nuclei were atrophic; the cells appeared degenerated and reduced in number. Preparations counterstained with red oil showed some macrophages laden with fat around the perivascular spaces.

SUMMARY

The histopathologic findings can be summarized as follows: diffuse degeneration of the cortex and white matter of the cerebral hemispheres, brainstem, and cerebellum. The atrophy of the cerebral cortex was very marked and accompanied by intense gliosis. In the white matter of the hemispheres there was a severe demyelinization with a marked spongy state, gliosis, proliferation of large astrocytes, and abundant microglia (gitter cells). The "U" fibers did not appear to be involved in the pathologic process and there was no evidence of inflammatory reaction. Throughout the brainstem there was degeneration of the gray matter affecting mainly the cranial nerve nuclei and pontine nuclei, along with demyelinization of the descending pathways, particularly the motor tracts. In the cerebellum there was marked atrophy of the cortex, with loss of granular cells and almost complete loss of Purkinje cells. Intense gliosis, demyelinization, and spongy state were noted in the white matter.

The different types of cerebral degeneration in childhood have been described. These conditions are so diversified and our knowledge of them is so incomplete that adequate classification is not possible. Nevertheless, it is possible to distinguish certain groups even though their limits are not precise.

The intense and diffuse degenerative process of the gray and white matter of the brain in the case presented appears like a summation of the lesions described separately in two different conditions. On one hand, the diffuse degeneration of the gray matter of the cerebral hemispheres, brainstem, and cerebellum resembles very much that in the

cases described by Alpers and Ford, in which they found similar lesions in the gray substance, but minimal involvement of the white matter. On the other hand, the intense demyelinization and spongy state of the white matter of the brain in the present case resembles the changes found in that group of demyelinating disease known as diffuse sclerosis, and in particular encephalitis periaxialis diffusa of Schilder. It differs, however, by the presence of intense degeneration of the gray matter of the cortex and brainstem, and particularly by such changes in the cerebellum, which is usually unimpaired in Schilder's disease.

Clinically the case resembles more the infantile cases of Schilder's disease. The onset, with disturbances of motility, spasticity, incoordination, tremor, loss of speech and sight, pseudobulbar symptoms, and convulsions seem to favor this diagnosis. However, the pathologic findings are more extensive and include also the gray matter.

In view of these facts, it is a problem to find a single diagnostic label for the case under discussion. It could best be considered a transitional type between the encephalitis periaxialis diffusa of Schilder and the diffuse degeneration of the cerebral gray matter of Alpers.

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■ *Which part of the gray matter is employed in the transmission of sensitive impressions?* This substance is composed of parts surrounding the central canal of the cord, of lateral masses, and of two anterior and two posterior horns, which separate the lateral columns from the anterior and the posterior ones. I call central gray matter the lateral masses, the bases of the anterior and posterior horns, and all the substance around the central canal, and I think that the transmission of the sensitive impressions takes place chiefly by this central grav matter. As regards the anterior horns of gray matter, I am not prepared to affirm that they have no share at all in this function; but I may state the posterior horns do not participate in it, in the same way as the central portion of gray matter.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CASE REPORT

Olivopontocerebellar Atrophy

John R. Geary, Jr., M.D., Ph.D., Kenneth M. Earle, M.D. and Augustus S. Rose, M.D.*

SINCE THE PUBLICATION in 1900 of the report by Dejerine and Thomas[1] describing a peculiar, selective degeneration of certain elements in the cerebellum, pons, and medulla oblongata, approximately 45 cases designated or suggested as representing examples of olivopontocerebellar atrophy have been reported in the world literature. A number of these cases have been so designated on the basis of clinical findings alone. In fact, the second case of Dejerine and Thomas was alive at the time of the report and was included only because of the similarity in clinical findings to their previous case which had come to autopsy.

During the ensuing years the concept has gradually emerged of two separate pathologic entities involving atrophy of structures in this region, the olivopontocerebellar variety and primary cerebellar atrophy.[2,3] There appears to be some justification on embryologic grounds for separating olivopontocerebellar atrophy as a distinct pathologic entity, since it has been shown by Essick[4,5] that the neurons of the inferior olivary nuclei, arcuate nuclei, and pontine nuclei have a common origin in the rhombic lip of the fourth ventricle. It is widely accepted that the primary process in olivopontocerebellar atrophy occurs in these nuclei, and that the diminution in size of the cerebellum is secondary. Degeneration of specific areas of the cerebellar cortex has been described following lesions in various portions of the inferior olives.[6] On the other hand, in primary cerebellar atrophy the involvement of the inferior olivary nuclei appears to be secondary to cerebellar degeneration.[2,3]

Considerable confusion still exists, however. Some authors continue to place all cases of cerebellar atrophy into a single group,[7–11] and others designate cases with widespread involvement of many diverse systems in the central nervous system as olivopontocerebellar atrophy.[12,13] In some reports the clinical histories are inadequate.[14] Finally, cases designated as either olivopontocerebellar atrophy or primary cerebellar atrophy continue to appear in the literature in which the diagnosis has been made on the basis of purely clinical findings,[13,15–17] and yet there is no general agreement that a precise clinical picture is associated with either disease.

Because of the lack of agreement regarding the nature, classification, and incidence of the cerebellar atrophies, it is considered

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appropriate to report an isolated case in which detailed clinical and postmortem examinations were obtained. The following case was first observed at the Los Angeles Veterans Administration Medical Center in 1943, and followed for ten years until the patient's death on January 13, 1953.

CLINICAL HISTORY

The patient was a 66 year old white male gardener who first sought medical care at the age of 57 because of stiffness of the legs and difficulty in walking. Family history was incomplete. His father died when the patient was 12 years of age, cause of death unknown, and his mother died during the patient's infancy. A brother died in 1917. The patient had measles, mumps, and chickenpox in childhood without complications. He was a veteran of World War I and spent approximately a year in service without overseas duty. He drank moderately between the ages of 20 and 30 but not thereafter. He smoked about a half package of cigarettes per day.

At the time of the initial examination in 1943 his blood pressure was 145/80 and pulse 72. A tremor was present in the hands. Some stiffness was noted in the legs. Unsteadiness was present in the performance of the Romberg test. No other neurologic abnormalities were recorded. Serology and routine blood and urine examinations were within normal limits.

His course during the next few years was characterized by gradually increasing difficulty in walking and he became confined to a wheelchair. He experienced occasional episodes of dizziness. Weakness in his arms and hands appeared after the disturbance in his legs. In 1948, about five years after the onset of his illness, he began having difficulty with speech and about the same time an increasingly severe intention tremor of his hands was noticed.

Physical examination in 1949 revealed a well developed, poorly nourished white male appearing older than his stated age of 63. He was oriented, cooperative, and there was no significant mental deterioration. Visual acuity was normal and visual fields were intact. There was no optic atrophy. Mild senile macular degeneration and moderately severe retinal arteriosclerosis were observed. Pupils were small, equal, slightly irregular, and they reacted to light and accommodation. The extraocular muscles were normal and there was no diplopia. There was severe nystagmus in gazing in all directions, with quick component in direction of gaze. Corneal reflexes were hypoactive but equal. There was no sensory impairment of the face. Palate arched symmetrically, although the gag reflex was reported to be absent. There was no dysphagia. Speech was dysarthric. At times it was reported as tremulous, muffled, indistinct, and as having a nasal quality. The tongue protruded in the midline and showed no atrophy or fasciculation. Neck and shoulder girdle muscles were normal. There was generalized weakness and hypotonia. Stretch reflexes were present, hypoactive, and equal. Abdominal reflexes were symmetrically present. Cremasterics could not be elicited. No Babinski or other pathologic toe signs were elicited. No abnormality of the sensory examination was recorded.

Marked incoordination of the extremities was noted in the performance of alternating movements. Severe intention tremor (finger-to-finger, finger-to-nose, heel-to-shin tests) was demonstrated. No evidence of rigidity was elicited. The patient was confined to a wheelchair and a description of gait was not given.

Examination in September 1952 revealed a thin, poorly nourished, cachetic white male sitting in a wheelchair. His speech was extremely difficult to understand because of its scanning, monotonous, and interrupted nature. Even while in the sitting position there was a teeter-tottering incoordination of the trunk, especially to the right. In addition, the following abnormalities were present: The right pupil was smaller than the left and was apparently fixed to light. There was a nystagmoid movement of the eyes upon lateral gaze. The gag reflex was absent bilaterally. The patient alleged no difficulty in swallowing foods. There was marked slowness in voluntary movement of the extremities and there was definite weakness of all muscle groups. Muscle tone was reduced. Position, vibratory, tactile, and pain modalities were intact. The biceps reflexes were equal bilaterally. The radials were absent bilaterally. The patellar and Achilles reflexes were absent bilaterally. Plantar reflexes were normal. Coordination tests, such as finger-to-finger and finger-to-nose, were performed poorly. Station and gait were not tested.

His terminal course was characterized by recurrent urinary tract infections. In the last week of life he developed bronchopneumonia and expired on January 13, 1953.

POSTMORTEM EXAMINATION

At postmortem examination bronchopneumonia in both lower lobes and large amounts of white, semisolid exudate in the bronchi and trachea were found. The bladder was dilated and contained about 500 cc. of clear, yellow urine. The wall was markedly trabeculated with a number of diverticula, the largest of which

measured 2 cm. in diameter. The mucous membrane was pale gray and smooth. There was bilateral chronic pyelonephritis and a small superficial abscess in the cortex of the left kidney. Incidental findings were a nodular hyperplasia of the thyroid, fibrotic scars at the lung apices, chronic cholecystitis, and melanosis coli.

Gross description of central nervous system

The scalp, calvarium, and dura were not remarkable. The leptomeninges showed slight thickening and opacity over the pons, cerebellum, and basal cisterns. The cerebral hemispheres were symmetric and showed no gross abnormality except slight cortical atrophy in both frontal regions. The vessels constituting the Circle of Willis had a few yellow atheromatous plaques in their walls without significant narrowing or calcification. The basilar artery likewise had a few plaques but was widely patent. The superior cerebellar, anterior inferior cerebellar, and posterior inferior cerebellar arteries were not remarkable. The pons, inferior olives, and all lobes of the cerebellum showed extreme generalized atrophy. This atrophy was grossly symmetric and affected all lobes and all surfaces of the cerebellum. There was no sparing of particular areas and the atrophy was not in the distribution of any particular artery or vein.

The brain weighed 1,340 gm. with the brainstem and cerebellum attached. The brainstem was removed by severing the peduncles transversely. The brainstem and cerebellum weighed 70 gm. (A normal brainstem and cerebellum from a man of nearly the same age, embalmed in the same manner, weighed 190 gm.) The difference in size and gross appearance of the brainstem and cerebellum of this case and the normal comparison are shown in figure 1.

Transverse sections of the brainstem and cerebellum were made at approximately 3 mm. intervals. These showed marked atrophy of the inferior olives, the basilar part of the pons, and all lobes of the cerebellum. The inferior and middle cerebellar peduncles showed marked atrophy, but the superior cerebellar peduncle was of usual size. The substantia nigra appeared less pigmented than usual and the cerebral peduncles showed slight generalized atrophy. The cerebellar folia were markedly narrowed and the sulci and fissures were widened. The fourth ventricle was enlarged. The cerebral aqueduct was slightly enlarged. The dentate nuclei, superior cerebellar peduncles (brachium conjunctivum), and the red nuclei showed no gross evidence of atrophy.

Microscopic description of central nervous system

Sections taken at 3 mm. intervals through the entire brainstem and cerebellum were studied in hematoxylin and eosin, Nissl, and Weil preparations. These showed atrophy and complete loss of neurons in the ventral (basilar) pons, both inferior olives, accessory olives, and arcuate nuclei. The longitudinal tracts and tegmentum of the pons were preserved, but the transverse fibers to the middle and inferior cerebellar peduncles were demyelinated and showed loss of fibers (figure 2).

Purkinje cells were absent in most of the cerebellar folia. A few Purkinje cells were scattered in some areas, but these showed no definite distribution. A few were spared at the crown of a gyrus, others were found in the depths of a sulcus. The nodulus contained more Purkinje cells than any other area, but it was severely atrophied as well. There was marked astrocytic gliosis in regions of nerve cell loss.

The granule cells were moderately reduced in numbers in the atrophic cerebellar folia. The basket and stellate cells of the molecular layer were not stained specifically, but their nuclei appeared to be present in the usual numbers in hematoxylin and eosin and Nissl stains. The Bergmann glia showed marked proliferation with clusters where Purkinje cells were lost.

The white matter of the cerebellum showed marked, but incomplete, demyelinization and apparent loss of axis cylinders in all folia studied. There was marked astrocytic gliosis in the areas of demyelinization.

Both middle and inferior cerebellar peduncles showed atrophy, incomplete demyelinization, reduction in fibers, and astrocytic gliosis. The superior cerebellar peduncles were remarkably preserved and showed no atrophy or demyelinization. The dentate nuclei were well preserved except for an increase of lipochrome pigment in the cytoplasm of the nerve cells. The red nuclei were well preserved. The emboliform, globose, and fastigial nuclei showed a slight reduction in the number of neurons present and slight astrocytic gliosis.

Description of remainder of central nervous system

Substantia nigra – small focal losses of neurons and astrocytic gliosis were noted. In some areas there were collections of free melanin pigment in areas of nerve cell loss. Several of the neurons in the substantia nigra showed curious, round, eosinophilic inclusion bodies in their nuclei, but none showed inclusion bodies in the cytoplasm like those seen in cases of postencephalitic parkinsonism. We have seen these inclusions in patients having no clinical symptoms. We do not know their significance, but have considered them as products of degeneration.

Basis pedunculi – the regions of the frontopontine and temporopontine tracts, seen in

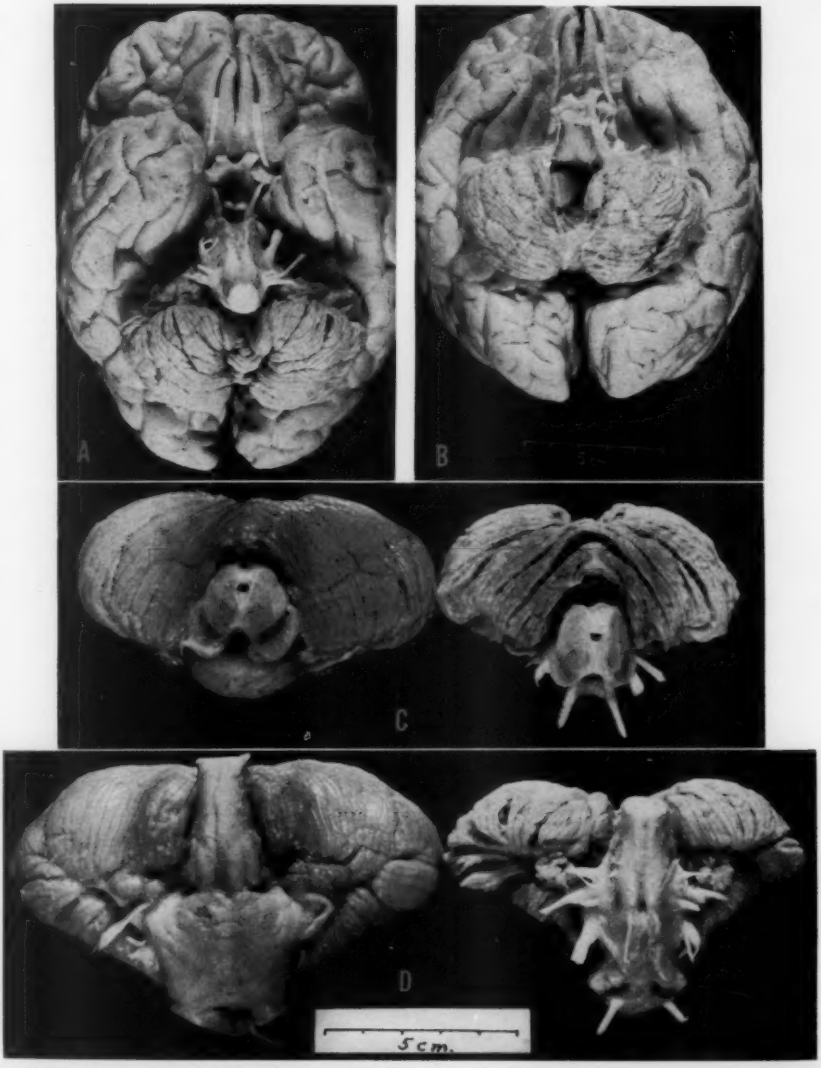

FIG. 1. Olivopontocerebellar atrophy. *A* and *B*. Two views of whole brain showing atrophy of cerebellum and brainstem. *C* and *D*. Superior and anterior views of atrophied cerebellum and brainstem are shown on the right compared with normal specimens on the left.

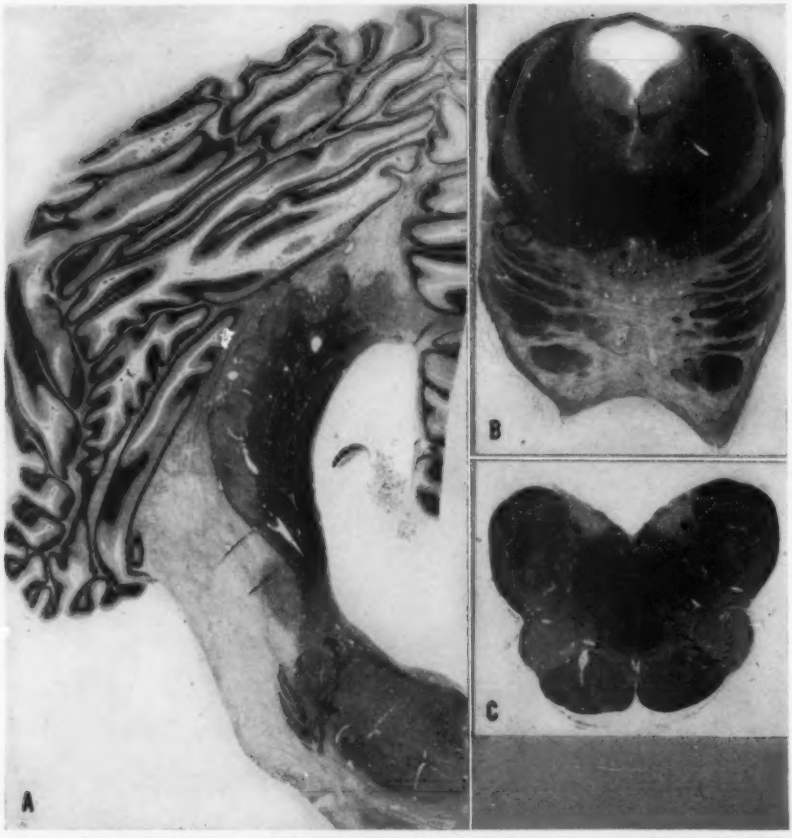

FIG. 2. Sections through pons, medulla, and cerebellum in a case of olivopontocerebellar atrophy. Weil stain. *A.* Section showing marked atrophy and demyelinization of cerebellar cortex and middle cerebellar peduncle. Note preservation of dentate nucleus and superior cerebellar peduncle. *B.* Section through pons showing marked atrophy and demyelinization of transverse fibers of pons and pontine nuclei with preservation of brachium conjunctivum and pontine tegmentum. *C.* Section through midolivary region of medulla showing marked atrophy of inferior olives and irregular atrophy of inferior cerebellar peduncles. Note loss of olivocerebellar fibers.

cross section in the midbrain, showed slight evidence of partial demyelinization and astrocytic gliosis. The region of the corticospinal and corticobulbar tracts appeared to be preserved.

Cranial nerve nuclei – none of the cranial nerve nuclei in the midbrain, pons, or medulla appeared to be involved.

Putamen – small focal areas of old encephalomalacia with astrocytic gliosis surrounding these areas were noted. The penetrating vessels showed moderate arteriosclerosis with widening of the perivascular spaces. The neurons appeared to be slightly reduced in numbers bilaterally.

Globus pallidus and caudate nuclei – not remarkable for his age.

Thalamus, hypothalamus, and subthalamus – not remarkable.

Cortex – generalized increase of lipochrome pigment in the neurons and scattered subpial amyloid bodies were noted.

Spinal cord – some demyelinization in the posterior white columns with slight astrocytic gliosis was present. There was an unusual number of amyloid bodies, particularly in the tractus gracilis. The neurons of Clarke's column appeared to be well preserved except for an increase of lipofuscin in the cytoplasm.

DISCUSSION

For the purpose of encouraging a more uniform and adequate method of reporting the clinical and pathologic manifestations in this group of conditions, Lichtenstein has proposed an analytic scheme for describing such cases.[3] The principal features of the present case will be analyzed according to this method.

1. Distribution of involvement. The vermis was atrophic. The atrophy of the cerebellar cortex was grossly symmetric and no particular area or surface appeared to be spared. There was no evidence that the involvement lay in the distribution of a particular artery.

2. Degree of involvement. Complete loss of Purkinje cells had occurred in most cerebellar folia. An occasional Purkinje cell was observed but no significance could be attached to their distribution. The granule cells were moderately reduced. The basket and stellate cells of the molecular layer did not appear to be significantly reduced in number. The white matter showed incomplete demyelinization and apparent nerve fiber loss.

3. Uniformity of involvement. The involvement of the cerebellum seemed to affect the Purkinje cells to a greater degree than the granule cells, but both were affected. This was uniform in all sections studied, except for occasional sparing of one or two Purkinje cells in a folium. The olives and the basilar pons showed a complete and uniform loss of neurons.

4. State of involvement. In most areas the disease process appeared to be stationary, but in parts of the basilar pons and parts of the white matter of the cerebellum there were elongated microglial nuclei and scattered gitter cells without any focal areas of encephalomalacia. This suggests that some degree of the demyelinization process, which was probably secondary to the loss of neurons, was still in progress.

5. Nature of involvement. This process appears to be a nonspecific progressive degeneration of neurons with secondary loss of axis cylinders and myelin sheaths. There was no evidence of inflammation or vascular disease. Since there was complete loss of neurons in the pontile and olivary nuclei and almost complete loss of Purkinje cells, it is difficult to determine whether one process preceded the other or whether primary degenerative changes occurred in both areas simultaneously. It is possible that the loss of some of these cells could have been the result of trans-synaptic degeneration, but with the evidence at hand such a mechanism can neither be proved nor excluded. Inflammation or arteriosclerosis does not appear to be an etiologic factor.

6. Origin of involvement. The origin of this involvement seems to be a primary degeneration of the olivary, pontile, arcuate nuclei, and cerebellar cortex. The possibilities of trans-synaptic degeneration are discussed above.

7. Secondary involvement. Dentate nuclei – not involved. Superior cerebellar peduncles – not involved. Red nuclei – not involved.

8. Associated involvement. Except for slight demyelinization of the posterior white columns of the spinal cord, there was no significant associated involvement.

9. Complicating pathology at site of involvement. Except for slight arteriosclerotic changes, there was no evidence of complicating pathology. The small areas of malacia in the putamen were too small to have caused significant alterations.

10. Pathogenesis. The etiology and pathogensis of the disorder observed in this case remains completely obscure. It was not possible to obtain an adequate family history so that heredofamilial factors cannot be evaluated. Although there is a history of moderate alcoholism at one period in this

patient's life, apparently this was not a problem after the age of 30. There was no history of excessive smoking, unusual infections, or trauma.

11. Symptomatology of the disorder. Clinically, the patient presented a progressive cerebellar type of ataxia without evidence of feeblemindedness, epilepsy, or significant mental deterioration. The disorder first manifested itself at about the age of 57 with difficulty in walking. It progressed steadily and relentlessly during the ensuing years with death occurring approximately ten years following the appearance of the initial symptoms.

12. Familial and hereditary factors. These could not be evaluated.

SUMMARY

A case of olivopontocerebellar atrophy was followed clinically for the entire ten year duration of the illness and confirmed by postmortem pathologic examination. No significant etiologic factor could be found for the profound degeneration of neurons in the pons, olivary nuclei, and cerebellar cortex. No significant pathologic changes were found elsewhere in the central nervous system.

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PROGRAM OF THE
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Eighth Annual Meeting

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Review Courses in Basic and Clinical Neurology

April 23, 24, 25, 1956

Intensive review courses in basic and clinical neurology will be given preceding the annual meeting, sponsored and arranged by the American Academy of Neurology. Courses will be held as follows:

Neuropathology—April 23, 1956

Infectious Diseases in Neurology—April 23, 1956.

Neurophysiology—April 23 and 24, 1956

Clinical Electroencephalography and Electromyography—April 24, 1956

Convulsive Disorders—April 24, 1956

Neurologic Disorders of Infancy and Childhood—April 24, 1956

Neurochemistry—April 25, 1956

Current Advances in Neurology—April 25, 1956

Injuries to the Nervous System—April 25, 1956

Additional information regarding these review courses may be obtained from Mrs. J. C. McKinley, Executive Secretary, 3501 East 54th Street, Minneapolis 17, Minnesota.

THURSDAY, APRIL 26, 1956

Morning Session 9:00 a.m.

Chairman: Richard B. Richter, *Chicago, Illinois*

Secretary: Ralph Druckman, *Houston, Texas*

Hamartoma of the Hypothalamus Causing a Syndrome of Precocious Puberty and Petit Mal Epilepsy with Paroxysmal Laughter

C. F. List, *Grand Rapids, Michigan*, and Jose Bebin, *Ann Arbor, Michigan*

Brain Swelling of Unknown Cause (Pseudotumor Cerebri)

A. L. Sahs and R. J. Joynt, *Iowa City, Iowa*

Pediatric Neuroophthalmology

Robert W. Hollenhorst, *Rochester, Minnesota*

Problems in Differential Diagnosis in Patients with Coexisting Neurological and Neurosurgical Disorder

Benjamin Boshes and Walter Hummel, *Chicago, Illinois*

Seizure States and Pregnancy

Cary Suter and Walter Klingman, *Charlottesville, Virginia*

Current Status of the Administration of Anticoagulant Drugs in Treatment of Certain Types of Cerebral Vascular Disease

C. H. Millikan, R. G. Siekert, J. P. Whisnant and R. M. Shick, *Rochester, Minnesota*

Present Status of Surgical Therapy for Extrapyramidal Disorders

H. Houston Merritt, *New York City*

Business Session 11:30 a.m.

Walter O. Klingman, presiding

THURSDAY, APRIL 26, 1956

Afternoon Session 2:00 p.m.

Chairman: Joe R. Brown, *Rochester, Minnesota*

Secretary: James A. Bastron, *Rochester, Minnesota*

Neurologic Sequelae Following Cardiac Arrest

Hugh E. Stephenson, *Columbia, Missouri*

Progressive Muscular Atrophy Secondary to Hyperfunctioning Pancreatic Adenoma

Donald W. Mulder, James A. Bastron and Edward H. Lambert, *Rochester, Minnesota*

Changes in the Glycoproteins of the Cerebrospinal Fluid in Neurologic Diseases

R. R. Apostol, E. Roboz, W. C. Hess and F. M. Forster, *Washington, D.C.*

The Central Nervous System in Carbon Tetrachloride Intoxication

Maynard M. Cohen, *Minneapolis, Minnesota*

Centrencephalic Epilepsy: Genetic and Electroencephalographic Studies

J. D. Metrakos and Katherine Metrakos, *Montreal, Canada*

Retinal Artery Pressure Measurements in the Diagnosis of Cerebral Vascular Disease Caused by Occlusion of the Internal Carotid Artery

Albert Heyman, Herbert R. Karp and Byron M. Bloor, *Durham, North Carolina*

Lipemia in Experimental Allergic Encephalomyelitis

Elizabeth Roboz, Marian W. Kies, Norman P. Goldstein and Joseph B. Murphy, *Washington, D.C.*

Effect of Metabolic and Electrolyte Disturbance upon the Human Electroencephalogram

Peter Kellaway, F. J. Moore and H. Conn, *Houston, Texas*

THURSDAY, APRIL 26, 1956

Evening Session 8:00 p.m.

A SYMPOSIUM OF INQUIRY

What We Need to Know About the Pyramidal System

This is a prepared two-hour discussion by four eminent scientists, designed to summarize knowledge of the pyramidal system and emphasize the areas where more research is needed. Written questions from the floor will be encouraged and answered by the panel. Speakers will be:

A. M. Lassek—Anatomy

Clinton Woolsey—Physiology

Benjamin Boshes—Clinical Neurology

A. Earl Walker—Clinical Neurophysiology and Neurosurgery

This is the second symposium of inquiry sponsored by the research committee of the American Academy of Neurology. It is intended to stimulate thinking and provoke research ideas.

FRIDAY, APRIL 27, 1956

Morning Session 9:00 a.m.

Chairman: Ephraim Roseman, *Louisville, Kentucky*

Secretary: Richard C. Turrell, *Louisville, Kentucky*

Laughter in Epilepsy

Ralph Druckman and Dora Chao, *Houston, Texas*

Aphasia in Children, Diagnosis and Therapy

Frank R. Kleffner and Mildred A. McGinnis, *St. Louis, Missouri*

Electrophysiologic Study of a Case of Tay-Sachs Disease

Frank Morrell and Fernando Torres, *Minneapolis, Minnesota*

Use of Miltown in Convulsive and Related Disorders

M. A. Perlstein, *Chicago, Illinois*

Psychomotor Seizures in Childhood

Gilbert H. Glaser and Morris S. Dixon, *New Haven, Connecticut*

Hearing and Speech in Patients with Infantile Hemiplegia Before and After Left Hemispherectomy

Robert Goldstein, Allan C. Goodman and Robert B. King, *St. Louis, Missouri*

Some Problems in the Pathology of Mental Deficiency with Microcephaly

Orville T. Bailey and John S. Woodard, *Indianapolis, Indiana*

Business Session 11:30 a.m.

Walter O. Klingman, presiding

FRIDAY, APRIL 27, 1956

Afternoon Session 2:00 p.m.

Chairman: A. Theodore Steegmann, *Kansas City, Kansas*

Secretary: John A. Segerson, *Topeka, Kansas*

Ultrasound in Neurology

William J. Fry, *Urbana, Illinois*

Psychic Seizures

Ernst A. Rodin, *Ann Arbor, Michigan*

Cingulate Gyrus Seizures

O. J. Andy and R. McChinn, *Jackson, Mississippi*

Variations in Consciousness Produced by Stimulation of Areas of the Reticular Substance of the Unanesthetized Rhesus Monkey

Lorne D. Proctor, Robert S. Knighton and John A. Churchill, *Detroit, Michigan*

The Structural Spread of Cortically Induced Epileptic Discharge

A. E. Walker and G. F. Poggio, *Baltimore, Maryland,* and O. J. Andy, *Jackson, Mississippi*

Movements of the Face and Jaw During Epileptiform Discharge in the Temporal Regions

Maitland Baldwin, Laurence L. Frost and Charles D. Wood, *Bethesda, Maryland*

Complications of Cerebral Arteriography in 325 Cases

David R. Coddon and Howard P. Krieger, *New York City*

Some Cerebellocerebral Functional Relationships

Ray S. Snider, *Chicago, Illinois*

SATURDAY, APRIL 28, 1956

Morning Session 9:00 a.m.

Chairman: Russell N. DeJong, *Ann Arbor, Michigan*

Secretary: William W. Anderson, *Ann Arbor, Michigan*

Recognition and Management of Intracranial Sepsis

Simon Horenstein and Nelson Xavier, *Boston, Massachusetts*

Epilepsy and Life Insurance

Alex J. Arieff, *Chicago, Illinois*

Otitic Hydrocephalus

Sir Charles Symonds, *London, England*

Palatal Myoclonus

Christian Herrmann, Jr., Paul H. Crandall and Harry C. H. Fang, *Los Angeles, California*

Subarachnoid Hemorrhage: Clinical and Therapeutic Factors Affecting Prognosis

Louis L. Tureen, James F. Sullivan and Joseph F. Raleigh, *St. Louis, Missouri*

Pathologic Considerations in Internal Carotid Occlusion

Richard G. Berry and Bernard J. Alpers, *Philadelphia, Pennsylvania.*

Shift to Older Age Distribution in Parkinson's Disease. A Report on 1000 Patients Covering the Past Decade from Three Centers

Robert S. Schwab, *Boston, Massachusetts,* Lewis Doshay, *New York City,* Hugh Garland and Peter Bradshaw, *Leeds, England,* Eleanore Garvey, *Boston, Massachusetts,* and Betty Crawford, *New York City*

Large Intracranial Aneurysm Producing Panhypopituitarism and Frontal Lobe Syndrome

Philip G. Gallagher, Joseph Dorsey, Mario Stefanini and Joseph Looney, *Boston, Massachusetts*

The Cerebroautonomic and Myographic Changes Accompanying Induced Seizures

Jack M. Mosier, Philip White, Phyllis Grant, John E. Fisher and Richard Taylor, *New Castle, Indiana*

Further Observations on Craniovascular Studies

Percy Brazil and Arnold P. Friedman, *New York City*

READ BY TITLE

Cystericerosis of the Central Nervous System

Fernando Cabieses and Raul Jeri, *Lima, Peru*

Acetylcholinesterase Activity in the Cochlea

J. A. Churchill and H. F. Schuknecht, *Detroit, Michigan*

Changes Produced in the Central Nervous System of Suckling Mice and Hamsters by the Inoculation of the Serum and Cerebrospinal Fluid of Acute Multiple Sclerosis

T. Lehoczky, M. Lehoczky and E. Molnar, *Budapest, Hungary*

Anisocoria: Diagnosis and Clinical Significance of Pupillary Inequality

Otto Lowenstein, *New York City*

Definition of the Amyotrophic Lateral Sclerosis Syndrome

Edward P. Roemer, *Madison, Wisconsin*

The Convulsive State and Schizophrenia

M. P. Rosenblum, *Lyons, New Jersey*

Facial Paralysis in Poliomyelitis

Irving C. Sherman and S. J. Kimelblot, *Chicago, Illinois*

Disseminated Sclerosis. A Survey of Cases of Disseminated Sclerosis in the Kingston Area

Denis White, *Kingston, Ontario*

SCIENTIFIC PROGRAM COMMITTEE

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Neurology

BOOK REVIEWS

Brain Mechanisms in Diachrome

Wendell S. Krieg. 1953. Evanston, Illinois: Brain Books. 188 pages. $7.00.

THIS rather small book contains, in relation to its size, a very complete description of the structural organization and functional pattern of the nervous system. Three-dimensional illustrations are utilized constantly.

The feature of the book is the reconstruction of the brain in diachrome, printed on sheets of transparent cellulose acetate as a separate fascicle. This consists of six double sheets, the two sides of each depicting one group of structures as seen from the medial and one from the lateral view. The colors are remarkably brilliant, varied, and well reproduced. The author hopes that the work may present the structure and function of the brain to students in psychology, nurses, technicians, or may be useful as a supplementary reference to medical students and practicing physicians. In spite of the clarity of the style, teaching commentary would have to be supplied to some of these groups at least. It is a worthwhile acquisition to the library of any neurologist and, like the other works of the author, represents an artistic and literary achievement which may well place it among collectors' items in the future.

The author includes an introduction to the embryology of the human brain and to comparative neuroanatomy. In this connection it is gratifying to see that a description of a salamander brain is given, a tribute to Johnson, Herrick, and Coghill, who, as founding fathers of the American School of Comparative Neurology, utilized this indigenous amphibian for so much of their investigative work.

This book is distributed only on direct prepaid order to the publisher. The price is $7.00 singly, or $6.00 when ten or more are ordered.

A. B. V.

Surgery of the Sympathetic

Alexander Lee McGregor. 1955. Bristol: John Wright and Sons, Ltd. 192 pages. $7.00.

THE TITLE OF THIS BOOK gives a clue to its context and literary style. It is a terse, informal presentation of the general problems requiring surgery of the sympathetic nervous system with emphasis on the surgical anatomy and technic.

After a description of the topographic anatomy of the autonomic nervous system, the author proceeds to discuss the various syndromes of the extremities and trunk for which sympathectomy has been advocated. The clinical pictures depicted follow strictly orthodox patterns. The different operations upon the sympathetic nervous system are outlined with considerable emphasis on the surgical anatomy – a feature which younger surgeons will appreciate. Finally, essential

hypertension — a subject in which the author has had considerable experience — is discussed from the standpoint of diagnosis, prognostic factors, and indications for sympathetic surgery. The chapters on this subject are based to a large extent upon the author's personal experience and are the most interesting in the book.

Numerous line drawings illustrate the anatomy and surgical technic; some complement the text admirably. A list of references and an adequate index are included.

Most readers would agree with the author that the sympathetic nervous system is immensely complex, but few would concur, even after reading the monograph, that it is "as regards its practical applications . . . an essentially simple structure." Perhaps the author's thesis that there are very few "sympathetic operations," so they should be standardized and simplified, has some validity. Such standard operations may allow a more detailed and meaningful analysis of the limitations and end results of sympathetic surgery. Young surgeons will find in this volume hints which will be helpful at the operating table, but to the neurologist and internist the book has a limited appeal.

A. E. W.

Neurovascular Hila of Limb Muscles

James Couper Brash. 1955. Baltimore: Williams and Wilkins Co. 100 pages. $7.00.

THIS is a gross anatomic study undertaken to determine the extent to which the principal blood supply of the limb muscles is associated with nerves, that is, the constancy or otherwise of a definite "neurovascular hilum." From a clinical standpoint, the data are applicable in the diagnosis and treatment of peripheral nerve and vascular injuries.

The work is based on careful observations made in the dissecting room and checked against the findings of other principal investigators. These data are presented in carefully drawn illustrations; a complete table of the levels of nerve entry for all limb muscles provides a valuable summary of the details.

This book has much merit. Anatomic texts generally fail to locate the sites and places of entry of neurovascular structures into muscles. This monograph supplies the information graphically and precisely.

A. R. V.

Receptors and Sensory Perception

Ragnar Granit. 1955. New Haven: Yale University Press. 369 pages. $5.00.

THIS well written, but by no means exhaustive, treatise deals with the newer aspects of the neurophysiologic research of sensory functions as far as they have been obtained by electrophysiologic methods. The results of the study of the activity of the retina (including the retinogram) and of investigations on muscle spindles are emphasized. Discussion of the spontaneous activity of sense organs and of the role of the central nervous system in controlling peripheral sense organs is particularly interesting. The book is beautifully printed and is recommended to neurologists who wish to read an authoritative account of present day ideas and results of neurophysiologic research.

E. G.

Clinical Neurosurgery

Proceedings of the 1954 Congress of Neurological Surgeons. 1955. Baltimore: The Williams & Wilkins Company. 173 pages. $6.75.

AT THEIR annual meeting December 4 and 5, 1954, the Congress of Neurological Surgeons invited as guest of honor Dr. Kenneth G. McKenzie, "one of the philosophers in neurological surgery and perhaps the most thoughtful man in the field on the North American continent." The proceedings of this meeting contain Dr. McKenzie's addresses on intracranial astrocytomas, acoustic neuroma, surgical treatment of spasmodic torticollis, Ménière's syndrome, and trigeminal tractotomy. The last half of the book contains symposia on "Cervical Trauma" and "Medicolegal Aspects of Head Injury."

In Dr. McKenzie's dissertations is much practical advice for the neurosurgeon, which can be read with profit and interest by the neurologist. The viewpoints presented upon the various subjects are founded upon careful observations made over many years.

The symposia complement the clinical lectures, bringing forth the most recent advances and sometimes controversial views on the two subjects. While neither symposium constitutes a complete discussion of the topic, a great deal of excellent material is presented.

The text material is accompanied by well produced illustrations. A short but adequate index is appended.

This second volume of the Congress of Neurological Surgeons will be of much value to the practicing surgeon but should be read by all neurologists who desire to keep up with changing neurosurgical opinions, concepts, and practices.

A. E. W.

■ Experiments upon the medulla oblongata, to decide if the crossing of the conductors of sensitive impressions, coming from the trunk and limbs, has taken place before they reach this organ or not, cannot give positive results, because the reflex movements are so energetic after a section of a lateral half of this nervous centre, that it is very difficult to know the degree of sensibility. But pathological facts, observed in man, will settle the question, as we shall show in another lecture. We have not, however, to regret that experiments on the medulla oblongata are useless, as it seems that the question of the decussation of the conductors of sensitive impressions, as far as the trunk and limbs are concerned, is clearly solved by the experiments on the spinal cord.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

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MARCH, 1956

Conference on Training In Clinical Neurology

One hundred and twenty-five clinical neurology training program directors, prospective program directors, medical school deans, and medical educators have been invited to participate in a conference on training in clinical neurology (April 23) at the Jefferson Hotel, St. Louis, prior to the annual Academy meeting (April 26-28). The conference is being sponsored by the Neurology Training Grant Committee of the National Institute of Neurological Diseases and Blindness. Its purpose is to present the objectives and policies of the NINDB Graduate Medical Training Grant Program and to provide an opportunity for group discussion of problems encountered in the training of neurologists (see December 1955 Newsletter).... The morning (9:00 to 11:30 a.m.) program will open with introductory remarks by A. B. Baker, chairman of the NINDB Neurology Training Grant Committee, followed by presentations and discussions: Needs in the Field of Neurology (Pearce Bailey), Accomplishments of the Neurology Training Grant Program (Russell N. DeJong), Influence of Graduate Training Programs in Neurology on Undergraduate Medical Training (Francis M. Forster), and Administration of the Graduate Medical Training Program in Neurology, showing how to apply for a grant, use of funds, and methods of review of applications (Gordon H. Seger, Chief, Extramural Programs, NINDB). The afternoon session (2:00 to 5:00 p.m.) will highlight a panel discussion on problems encountered in neurologic education, with A. B. Baker serving as moderator.

New AAN Members From Abroad

Twenty-one distinguished foreign neurologists have been elected to honorary-corresponding membership in the AAN: Dr. Roman Arana-Iniguez (Uruguay), Dr. Ludo van Bogaert (Belgium), Prof. F. Bremer (Belgium), Prof. Vita Maria Buscaino (Italy), Dr. Jacob Chandy (India), Dr. Humberto Fernandez-Moran (Venezuela), Prof. Dr. E. Frauchiger (Switzerland), Prof. Henri Gastaut (France), Dr. Youssif H. Guinena (Egypt), Dr. L. Halpern (Israel), Prof. H. Hoff (Austria), Prof. Seizo Katsunuma (Japan), Prof. P. D'Almeida Lima (Portugal), Dr. Manuel de Rojas (Cuba), Prof. Dr. G. G. J. Rademaker (Holland), Prof. Sigvald Refsum (Norway), Prof. Dr. George Schaltenbrand (Germany), Dr. E. Tchehrazi (Iran), Dr. J. O. Trelles (Peru), Dr. Knud Winther (Denmark),

Prof. Dr. Gunnar Wohlfart (Sweden).... The group of honorary-corresponding members, who are distinguished neurologists outside of North America, now totals 47, representing 30 countries.

New AAN Junior Members Recent additions to junior membership in the Academy are: Stanley M. Ball, Albany, N. Y.; Bernard Cohen, New York City; William E. DeMyer, Indianapolis, Ind.; Gilbert S. Frank, Minneapolis, Minn.; Donald George Ives, Ann Arbor, Mich.; Lowell G. Lubic, Pittsburgh, Pa.; Richard W. Naef, Upper Darby, Pa.; Antonio Valdes Rodriguez, Ann Arbor, Mich.; Richard L. Roth, Ann Arbor, Mich.; Jose M. Segarra, Boston, Mass.; Joseph Shechtman, White Plains, N. Y.... Junior membership in the Academy is open to physicians in graduate training to become qualified clinical neurologists.... Annual dues (one-half of active membership) are $11.00, which includes subscription to the Academy's monthly journal, NEUROLOGY.... Requests for information or application blanks should be forwarded to Mrs. J. C. McKinley, AAN Executive Secretary, 3501 East 54th Street, Minneapolis 17, Minn.

New Diplomates in Neurology At the annual examination of the American Board of Psychiatry and Neurology held in New York City (Dec. 12-13), 18 candidates were certified in neurology. The successful candidates are: Gustav Walter Anderson, Hartford, Conn.; Leonard Berg, St. Louis; Malcolm B. Carpenter, New York City; Chester F. Cullen, Hartford, Conn.; J. Dana Darnley, Detroit; Thomas Murray Drisland, Albany, N. Y.; Daniel Solomon Feldman, Charleston, S. C.; Eli S. Goldensohn, New York City; Erwin M. Jacobs, West Hartford, Conn.; Kenneth Raymond Magee, Bethesda, Md.; John Thomas McHenry, Buffalo, N. Y.; John Stirling Meyer, Boston; Warren E. Porter, Fort Sam Houston, Texas; Lewis P. Rowland, New York City; Labe Charles Scheinberg, New York City; Walter R. Slade, Jr., Brooklyn; Bernard H. Smith, Buffalo; Robert R. J. Strobos, Winston-Salem, N. C.... The next Board examination will be held in Philadelphia April 15, 16, and 17.... Dr. Frederick P. Moersch, senior consultant in the section of neurology at the Mayo Clinic and professor of neurology in the Mayo Foundation Graduate School, University of Minnesota, was elected president of the American Board of Psychiatry and Neurology....

* * * * * *

Neurological Center Organized in Venezuela Under the auspices of the President of Venezuela, General Marcos Perez Jimenez, the Minister of Public Health, Dr. Pedro A. Gutierrez Alfaro, and Lewis L. Strauss, chairman of the U. S. Atomic Energy Commission, and in the presence of representatives of the diplomatic corps and scientific societies, the "pilot unit" of the Venezuelan Institute for Neurology and Brain Research was opened near Caracas (December 23, 1955). Director of the new program is Dr. Humberto Fernandez-Moran, formerly assistant professor in cell research at the Karolinska Institute

in Stockholm. The inauguration activities dedicated the opening of the laboratories for research in nerve ultrastructure, neurophysiology, biochemistry, biomathematics, a library, several workshops, and ten residential units for scientific personnel and assistants. To be added to the center, which stands 5,000 feet above sea level overlooking Caracas and encompasses 1,236 acres, is a large unit for neurotropic virus research, a radiation laboratory equipped with a nuclear reactor for medical research, and a group of buildings to house laboratories in biochemistry, biomathematics, experimental pharmacology, as well as a 200-bed hospital, designed along lines of the Clinical Center of the National Institutes of Health.... Conceived as an international research center which will be devoted mainly to fundamental research in the application of biophysics, biochemistry, and biomathematics to neurologic problems, the Venezuelan Institute of Neurology and Brain Research was founded with an initial grant of $1.6 million, which has now been supplemented by a further grant of $1.4 million. An agreement with the United States will provide the institute technical aid and certain radioactive material for medical research.... Information about the institute can be obtained through Prof. Humberto Fernandez-Moran, Director, Instituto de Venezolano, Neurologia e Investigaciones Cerebrales, Caracas, Venezuela.

Importance of Epidemiological Studies in Neurology Emphasized Among the recent recommendations of the AAN Committee on Nomenclature and Biometrics is the urgent need for obtaining more accurate statistical data on the incidence and geographic distribution of major neurologic disorders, considered by many as a relatively untapped field in neurologic research. To date the only investigations conducted have been those in multiple sclerosis and amyotrophic lateral sclerosis, which have set a pattern for more extensive surveys and resulted in interesting and pertinent findings on the geographic distribution and population selectivity of these disorders that are now being further explored through clinical, genetic, laboratory, and etiologic studies. According to Leonard B. Kurland, chairman of the AAN Committee on Nomenclature and Biometrics, there is a dearth of neurologists concerned with epidemiologic research, and the field abounds with unique opportunities. For example, physicians who intend to receive commissions in the Public Health Service should take advantage of this opportunity for additional training in clinical neurology and epidemiologic methodologies that would serve them well for teaching and research appointments in the medical centers to which they belong.

New MS Clinic Established The Chicago chapter of the National Multiple Sclerosis Society (53 W. Jackson Blvd.) announces the opening of a clinic for multiple sclerosis patients at St. Luke's Hospital, under the direction

of Roland P. Mackay, assisted by Donald D. Layton, resident neurologist at St. Luke's. The clinic will be open on Tuesday mornings and on Friday afternoons. Any members of the Chicago chapter of the National Multiple Sclerosis Society or patients with multiple sclerosis residing within the metropolitan area of Chicago may apply for admission after proper medical referral.

Houston Neurological Society Holds Scientific Session The fourth annual scientific session of the Houston Neurological Society was held on March 16 and 17 at the Texas Medical Center. The sessions, under Dr. Charles A. Carton as program chairman, were national in scope. The first day was devoted to a symposium on "Brain Mechanisms and Drug Action." The program included Neurophysiology of the Reticular System, Dr. Robert Livingston, department of anatomy, UCLA; The Effect of Drugs on the Reticular System, Dr. Harold E. Himwich, Galesburg State Research Hospital, Galesburg, Ill.; The Effect of Drugs on Neurons and Synapses, Dr. Amedeo S. Marrazzi, clinical research division, Army Chemical Center, Md., and Dr. Eva K. Killam, department of anatomy, UCLA; The Effect of Drugs on Behavior, Dr. Joseph V. Brady, Walter Reed Army Institute of Research; Summary of Day's Activities, Dr. Ralph W. Gerard, mental health research division, University of Michigan Hospital, Ann Arbor.... The second day was devoted to basic science and clinical papers in neurology, neurosurgery, and related disciplines.

Here and There Prof. Dr. G. Schaltenbrand, director of the University Neurological Clinic at Wurzburg, Germany, is making an extended lecture tour in the U. S., beginning March 4. The bulk of his lectures will be in the department of neurology of the University of California Medical Center (San Francisco), but he will also visit many major universities in the Pacific Northwest, Southern California, the Midwest, and terminate his trip at the AAN meeting in St. Louis and at the National Institute of Neurological Diseases and Blindness, Bethesda (the end of April).... Prof. Max Nonne, honorary-corresponding member of the Academy and honorary member of the ANA, celebrated his 95th birthday on January 13, 1956.... The medical faculty of the University of Zurich has established a department of neurology. Prof. Fritz Luthy, honorary-corresponding member of the Academy, is head of the new department.... Prof. W. Bartchi-Rochaix, formerly of the University of Bern, has accepted a full-time professorship in neurology at the University of Alexandria, Egypt.... Dr. Eduardo De Robertis, Instituto de Investigacion de Ciencias Biologicas, Montevideo, Uruguay, gave a special seminar on Submicroscopic Morphology and Morphogenesis of Retinal Rods, to the NINDB staff on February 3....

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[1]Am. J. Pharm.—117:319-326, 1945.
[2]N. Y. State Journal of Medicine 49/1285.
[3]Conference National Academy of Sciences Sept. 9, 1950.

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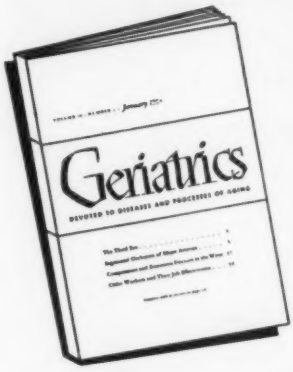

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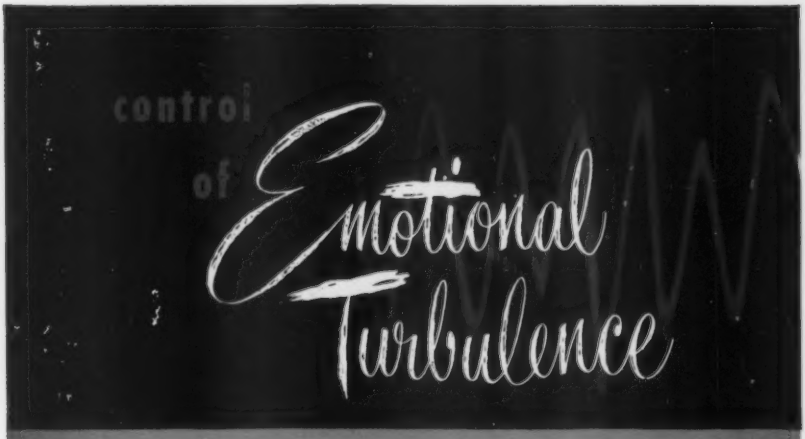

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